



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 401/12, 215/06, 471/04, 487/06</b>		<b>A1</b>	(11) International Publication Number: <b>WO 99/41251</b>
			(43) International Publication Date: 19 August 1999 (19.08.99)
(21) International Application Number: PCT/US99/02906 (22) International Filing Date: 10 February 1999 (10.02.99) (30) Priority Data: 60/074,413      11 February 1998 (11.02.98)      US 9805718.5      17 March 1998 (17.03.98)      GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): YOUNG, Jonathan, R. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GOULET, Mark, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WALSH, Thomas, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FISHER, Michael, H. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE			
<div style="text-align: center;"> <p>(I)</p> </div>			
(57) Abstract			
<p>There are disclosed compounds of formula (I) and pharmaceutically acceptable salts thereof which are useful as antagonists of GnRH and as such may be useful for the treatment of a variety of sex-hormone related illnesses and other conditions in both men and women.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**TITLE OF THE INVENTION****ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE****BACKGROUND OF THE INVENTION**

5           The gonadotropin-releasing hormone (GnRH), also referred to as luteinizing hormone-releasing hormone (LHRH), is a decapeptide that plays a key role in human reproduction. The hormone is released from the hypothalamus and acts on the pituitary gland to stimulate the biosynthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH released from the pituitary gland is primarily responsible for the regulation of gonadal steroid production in both sexes, whereas FSH regulates spermatogenesis in males and follicular development in females. GnRH agonists and antagonists have proven effective in the treatment of certain conditions which require inhibition of LH/FSH release. In particular, GnRH-based therapies have proven effective in the treatment of endometriosis, uterine fibroids, polycystic ovarian disease, precocious puberty and several gonadal steroid-dependent neoplasia, most notably cancers of the prostate, breast and ovary. GnRH agonists and antagonists have also been utilized in various assisted fertilization techniques and have been investigated as a potential contraceptive in both men and women. They have also shown possible utility in the treatment of pituitary gonadotrope adenomas, sleep disorders such as sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hyperplasia, hirsutism, as an adjunct to growth hormone therapy in growth hormone deficient children, and in murine models of lupus. The compounds of the invention may also be used in combination with bisphosphonates (bisphosphonic acids) and other agents, such as growth hormone secretagogues, e.g. MK-0677, for the treatment and the prevention of disturbances of calcium, phosphate and bone metabolism, in particular, for the prevention of bone loss during therapy with the GnRH antagonist, and in combination with estrogens, progestones, antiestrogens, antiprogestins and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with the GnRH antagonist.

10

15

20

25

30

35

Additionally, a compound of the present invention may be co-administered with a 5a-reductase 2 inhibitor, such as finasteride or epristeride; a 5a-reductase 1 inhibitor such as 4,7b-dimethyl-4-aza-5a-cholestan-3-one, 3-oxo-4-aza-4,7b-dimethyl-16b-(4-chlorophenoxy)-5a-androstane, and 3-oxo-4-aza-4,7b-dimethyl-16b-(phenoxy)-5a-androstane as disclosed in WO 93/23420 and WO 95/11254; dual inhibitors of 5a-reductase 1 and 5a-reductase 2 such as 3-oxo-4-aza-17b-(2,5-trifluoromethylphenyl-carbamoyl)-5a-androstane as disclosed in WO 95/07927; antiandrogens such as flutamide, casodex and cyproterone acetate, and alpha-1 blockers such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin.

Further, a compound of the present invention may be used in combination with growth hormone, growth hormone releasing hormone or growth hormone secretagogues, to delay puberty in growth hormone deficient children, which will allow them to continue to gain height before fusion of the epiphyses and cessation of growth at puberty.

Further, a compound of the present invention may be used in combination or co-administered with a compound having luteinizing hormone releasing activity such as a peptide or natural hormone or analog thereof. Such peptide compounds include leuporelin, gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterlin and recirelin.

Additionally, a compound of the present invention may be used as described in U.S. Patent No. 5,824,286 which discloses the administration of peptide GnRH antagonists such as Antide and azaline B to premenopausal women to enhance the readability of mammographic film relative to a mammogram effected in the absence of the administration.

Current GnRH antagonists are GnRH-like decapeptides which are generally administered intravenously or subcutaneously presumably because of negligible oral activity. These have amino acid substitutions usually at positions one, two, three, six and ten.

Non-peptide GnRH antagonists offer the possible advantage of oral administration. Non-peptide GnRH antagonists have been described in European Application 0 219 292 and in De, B. et al.,

J. Med. Chem., 32, 2036-2038 (1989), in WO 95/28405, WO 95/29900 and EP 0679642 all to Takeda Chemical Industries, Ltd.

Substituted indoles known in the art include those described in the following patents and patent applications. US Patent  
5 No. 5,030,640 discloses alpha-heterocyclic ethanol aminoalkyl indoles which are potent  $\beta$ -agonists. US Patent No. 4,544,663 discloses indolamine derivatives which are allegedly useful as male anti-fertility agents. WO 90/05721 discloses alpha-amino-indole-3-acetic acids useful as anti-diabetic, anti-obesity and anti-atherosclerotic agents. French  
10 patent 2,181,559 discloses indole derivatives with sedative, neuroleptic, analgesic, hypotensive, antiserotonin and adrenolytic activity. Belgian patent 879381 discloses 3-aminoalkyl-1H-indole-5-thioamide and carboxamide derivatives as cardiovascular agents used to treat hypertension, Raynaud's disease and migraine.

15

#### SUMMARY OF THE INVENTION

The present invention relates to compounds which are non-peptide antagonists of GnRH which can be used to treat a variety of sex-hormone related conditions in men and women, to methods for their  
20 preparation, and to methods and pharmaceutical compositions containing said compounds for use in mammals.

Because of their activity as antagonists of the hormone GnRH, the compounds of the present invention are useful to treat a variety of sex-hormone related conditions in both men and women.  
25 These conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as cancers of the prostate, breast and ovary, gonadotrophe pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy.  
30 They are also useful as an adjunct to treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosus. Further, the compounds of the invention may be useful in *in vitro* fertilization and as contraceptives. The compounds may also be useful in combination with androgens, estrogens, progesterones,  
35 antiestrogens and antiprogestogens for the treatment of endometriosis,

fibroids and in contraception. They may also be useful in combination with testosterone or other androgens or antiprogestogens in men as a contraceptive. The compounds may also be used in combination with an angiotensin-converting enzyme inhibitor such as Enalapril or Captopril, an angiotensin II-receptor antagonist such as Losartan or a renin inhibitor for the treatment of uterine fibroids. Additionally, the compounds of the invention may also be used in combination with bisphosphonates (bisphosphonic acids) and other agents, for the treatment and the prevention of disturbances of calcium, phosphate and bone metabolism, in particular, for the prevention of bone loss during therapy with the GnRH antagonist, and in combination with estrogens, progesterones and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with the GnRH antagonist.

Additionally, a compound of the present invention may be co-administered with a 5 $\alpha$ -reductase 2 inhibitor, such as finasteride or epristeride; a 5 $\alpha$ -reductase 1 inhibitor such as 4,7b-dimethyl-4-aza-5 $\alpha$ -cholestan-3-one, 3-oxo-4-aza-4,7b-dimethyl-16b-(4-chlorophenoxy)-5 $\alpha$ -androstane, and 3-oxo-4-aza-4,7b-dimethyl-16b-(phenoxy)-5 $\alpha$ -androstane as disclosed in WO 93/23420 and WO 95/11254; dual inhibitors of 5 $\alpha$ -reductase 1 and 5 $\alpha$ -reductase 2 such as 3-oxo-4-aza-17b-(2,5-trifluoromethylphenyl-carbamoyl)-5 $\alpha$ -androstane as disclosed in WO 95/07927; antiandrogens such as flutamide, casodex and cyproterone acetate, and alpha-1 blockers such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin.

Further, a compound of the present invention may be used in combination with growth hormone, growth hormone releasing hormone or growth hormone secretagogues, to delay puberty in growth hormone deficient children, which will allow them to continue to gain height before fusion of the epiphyses and cessation of growth at puberty.

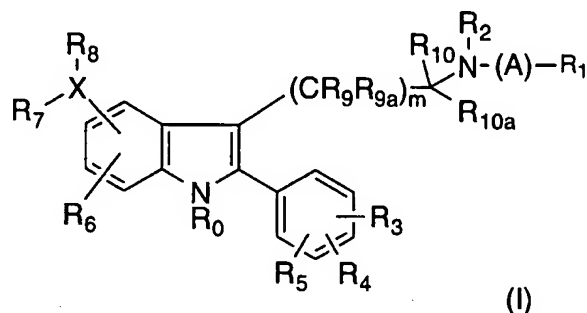
Further, a compound of the present invention may be used in combination or co-administered with a compound having luteinizing hormone releasing activity such as a peptide or natural hormone or analog thereof. Such peptide compounds include leuporelin,

gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterlin and recirelin.

Additionally, a compound of the present invention may be used as described in U.S. Patent No. 5,824,286 which discloses the administration of peptide GnRH antagonists such as Antide and azaline B to premenopausal women to enhance the readability of mammographic film relative to a mammogram effected in the absence of the administration.

## 10 DETAILED DESCRIPTION OF THE INVENTION

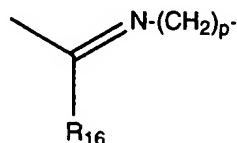
The present invention relates to compounds of the general formula



15 wherein

A is

C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, substituted C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, substituted C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl, substituted C<sub>3</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>0</sub>-C<sub>5</sub> alkyl-S(O)<sub>n</sub>-C<sub>0</sub>-C<sub>5</sub> alkyl, C<sub>0</sub>-C<sub>5</sub> alkyl-O-C<sub>0</sub>-C<sub>5</sub> alkyl, C<sub>0</sub>-C<sub>5</sub> alkyl-NR<sub>18</sub>-C<sub>0</sub>-C<sub>5</sub> alkyl where R<sub>18</sub> and the C<sub>0</sub>-C<sub>5</sub> alkyl can be joined to form a ring,

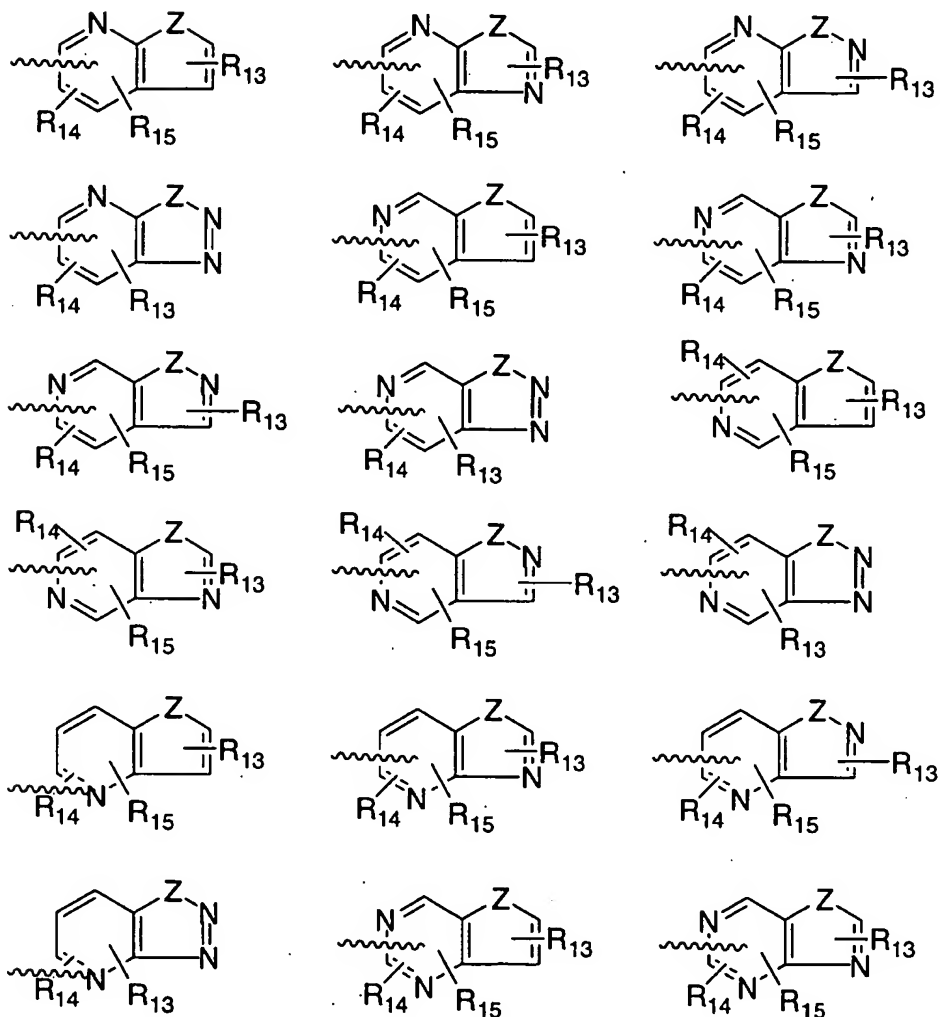


25

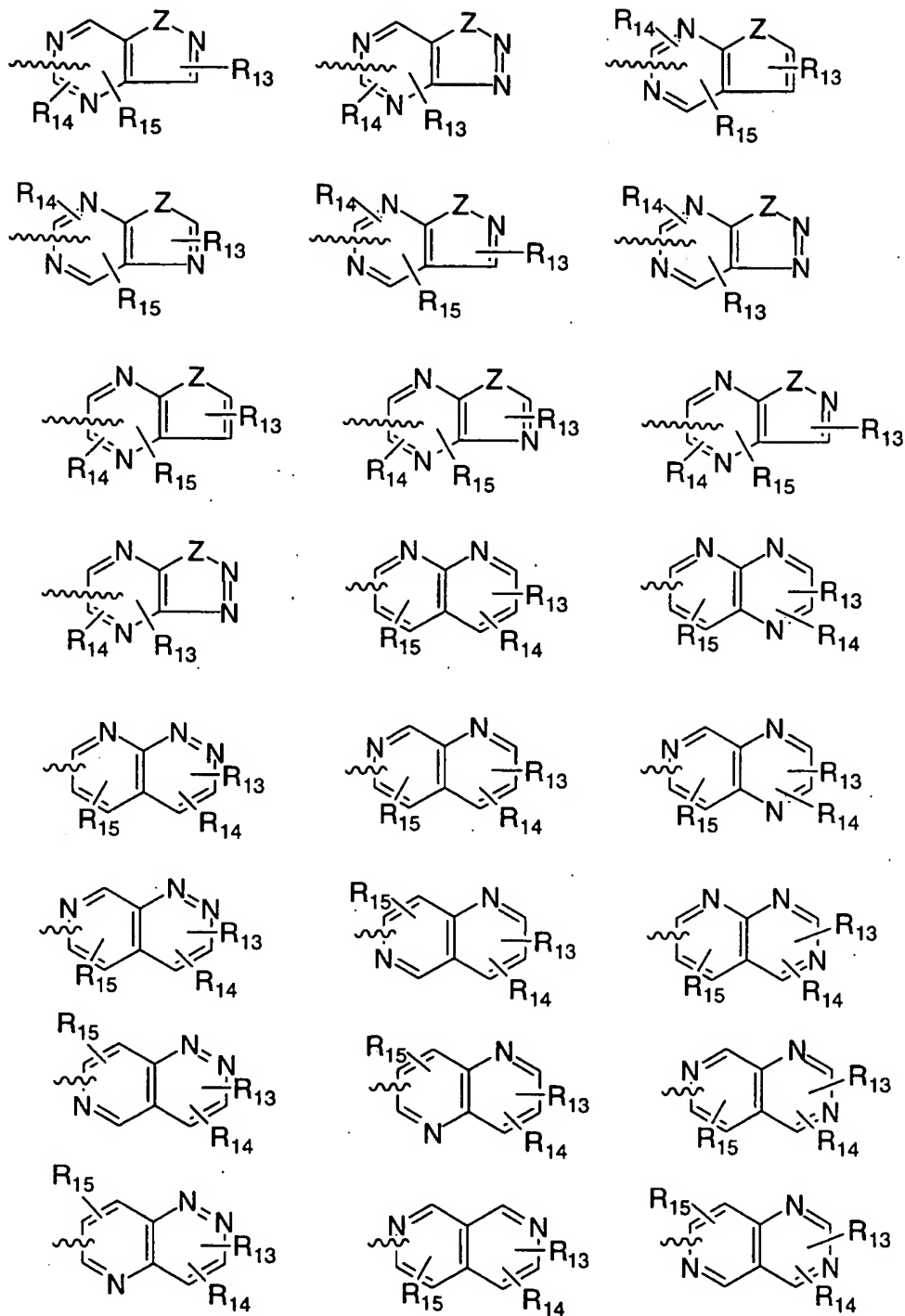
or a single bond;

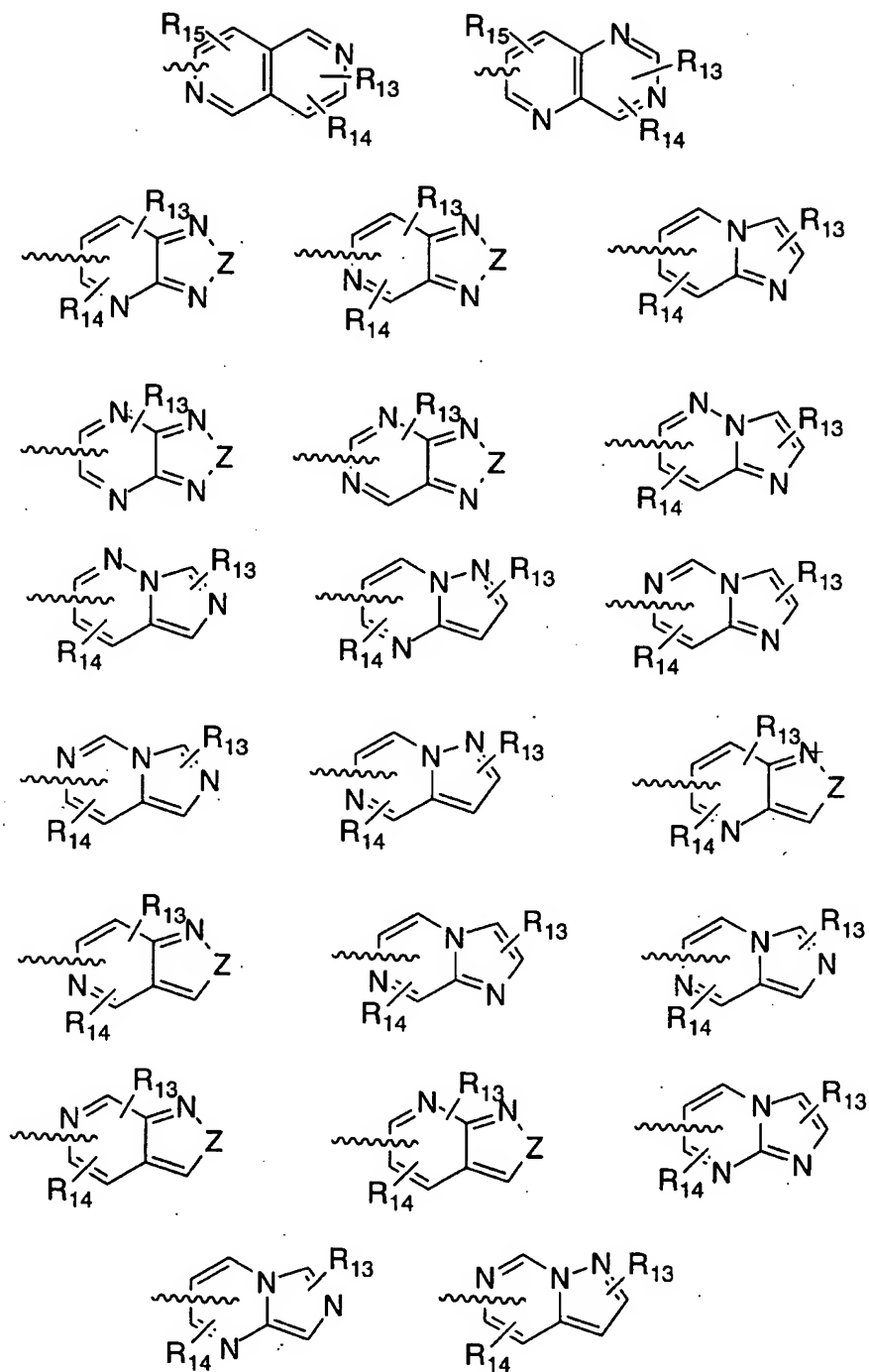
$R_0$  is hydrogen,  $C_1$ - $C_6$  alkyl, substituted  $C_1$ - $C_6$  alkyl, wherein the substituents are as defined below; aryl, substituted aryl, aralkyl or substituted aralkyl, wherein the substituents are as defined for  $R_3$ ,  $R_4$  and  $R_5$ ;

5  $R_1$  is









- R<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, alkyl -OR<sub>11</sub>, C<sub>1</sub>-C<sub>6</sub>(NR<sub>11</sub>R<sub>12</sub>), C<sub>1</sub>-C<sub>6</sub>(CONR<sub>11</sub>R<sub>12</sub>) or C(NR<sub>11</sub>R<sub>12</sub>)NH;
- R<sub>2</sub> and A taken together form a ring of 5-7 atoms;
- 5 R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, CN, nitro, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkoxy, aryl, substituted aryl, aralkyl, substituted aralkyl, R<sub>11</sub>O(CH<sub>2</sub>)<sub>p</sub>-, R<sub>11</sub>C(O)O(CH<sub>2</sub>)<sub>p</sub>-, R<sub>11</sub>OC(O)(CH<sub>2</sub>)<sub>p</sub>-, -(CH<sub>2</sub>)<sub>p</sub>S(O)<sub>n</sub>R<sub>17</sub>,  
 10 -(CH<sub>2</sub>)<sub>p</sub>C(O)NR<sub>11</sub>R<sub>12</sub> or halogen; wherein R<sub>17</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, aryl or substituted aryl;
- R<sub>3</sub> and R<sub>4</sub> taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing 1-3 heteroatoms selected from N, O and S;
- 15 R<sub>6</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, CN, NO<sub>2</sub>, halogen, R<sub>11</sub>O(CH<sub>2</sub>)<sub>p</sub>-, NR<sub>21</sub>C(O)R<sub>20</sub>, NR<sub>21</sub>C(O)NR<sub>20</sub>R<sub>21</sub> or SO<sub>n</sub>R<sub>20</sub>;
- R<sub>7</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, unless X is hydrogen or halogen, then R<sub>7</sub> is absent;
- 20 R<sub>8</sub> is C(O)OR<sub>20</sub>, C(O)NR<sub>20</sub>R<sub>21</sub>, NR<sub>20</sub>R<sub>21</sub>, C(O)R<sub>20</sub>, NR<sub>21</sub>C(O)R<sub>20</sub>, NR<sub>21</sub>C(O)NR<sub>20</sub>R<sub>21</sub>, NR<sub>20</sub>S(O)<sub>2</sub>R<sub>21</sub>, NR<sub>21</sub>S(O)<sub>2</sub>NR<sub>20</sub>R<sub>21</sub>, OC(O)R<sub>20</sub>, OC(O)NR<sub>20</sub>R<sub>21</sub>, OR<sub>20</sub>, SO<sub>n</sub>R<sub>20</sub>, S(O)<sub>n</sub>NR<sub>20</sub>R<sub>21</sub>, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl or substituted C<sub>1</sub>-C<sub>6</sub> alkyl; or
- 25 R<sub>7</sub> and R<sub>8</sub> taken together form a heterocyclic ring containing one or more heteroatoms selected from N, O or S which can be optionally substituted by R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>;
- 30 R<sub>9</sub> and R<sub>9a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl; aryl or substituted aryl, aralkyl or substituted aralkyl when m is not equal to 0; or

- R<sub>9</sub> and R<sub>9a</sub> taken together form a carbocyclic ring of 3-7 atoms or  $\text{O}=\text{C}$  when m is not equal to 0;
- R<sub>9</sub> and A taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms when m is not equal to 0; or
- 5 R<sub>10</sub> and R<sub>10a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl; or
- R<sub>10</sub> and R<sub>10a</sub> taken together form a carbocyclic ring of 3-7 atoms or  $\text{O}=\text{C}$ ;
- 10 R<sub>9</sub> and R<sub>10</sub> taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms when m is not equal to 0; or
- R<sub>9</sub> and R<sub>2</sub> taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms when m is not equal to 0; or
- 15 R<sub>10</sub> and R<sub>2</sub> taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;
- R<sub>10</sub> and A taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms; or
- 20 R<sub>11</sub> and R<sub>12</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic ring of 3-7 atoms or a substituted carbocyclic ring containing 3-7 atoms;
- R<sub>11</sub> and R<sub>12</sub> taken together can form an optionally substituted ring of 3-7 atoms;
- 25 R<sub>13</sub> is hydrogen, OH, NR<sub>7</sub>R<sub>8</sub>, NR<sub>11</sub>SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), NR<sub>11</sub>SO<sub>2</sub>(substituted C<sub>1</sub>-C<sub>6</sub> alkyl), NR<sub>11</sub>SO<sub>2</sub>(aryl), NR<sub>11</sub>SO<sub>2</sub>(substituted aryl), NR<sub>11</sub>SO<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl);
- SO<sub>2</sub>NR<sub>11</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), SO<sub>2</sub>NR<sub>11</sub>(substituted C<sub>1</sub>-C<sub>6</sub> alkyl), SO<sub>2</sub>NR<sub>11</sub>(aryl), SO<sub>2</sub>NR<sub>11</sub>(substituted aryl), SO<sub>2</sub>NR<sub>11</sub>(C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl);
- 30 SO<sub>2</sub>NR<sub>11</sub>(C(O)C<sub>1</sub>-C<sub>6</sub> alkyl); SO<sub>2</sub>NR<sub>11</sub>(C(O)-substituted C<sub>1</sub>-C<sub>6</sub> alkyl); SO<sub>2</sub>NR<sub>11</sub>(C(O)-aryl);

- SO<sub>2</sub>NR<sub>11</sub>(C(O)-substituted aryl); S(O)<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl); S(O)<sub>n</sub>(substituted C<sub>1</sub>-C<sub>6</sub> alkyl), S(O)<sub>n</sub>(aryl), S(O)<sub>n</sub>(substituted aryl), C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, COOH, halogen, NO<sub>2</sub> or CN;
- 5 R<sub>14</sub> and R<sub>15</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, CN, nitro, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkoxy, aryl, substituted aryl, aralkyl, substituted aralkyl, R<sub>11</sub>O(CH<sub>2</sub>)<sub>p</sub>-, R<sub>11</sub>C(O)O(CH<sub>2</sub>)<sub>p</sub>-, R<sub>11</sub>OC(O)(CH<sub>2</sub>)<sub>p</sub>-, -(CH<sub>2</sub>)<sub>p</sub>S(O)<sub>n</sub>R<sub>17</sub>, -(CH<sub>2</sub>)<sub>p</sub>C(O)NR<sub>11</sub>R<sub>12</sub> or halogen; wherein R<sub>17</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, aryl or substituted aryl;
- 10 R<sub>16</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or N(R<sub>11</sub>R<sub>12</sub>);
- 15 R<sub>18</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C(O)OR<sub>11</sub>, C(O)NR<sub>11</sub>R<sub>12</sub>, C(O)R<sub>11</sub>, S(O)<sub>n</sub>R<sub>11</sub>;
- R<sub>19</sub> is either the definition of R<sub>13</sub> or R<sub>14</sub>;
- R<sub>20</sub> and R<sub>21</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic ring of 3-7 atoms, a substituted carbocyclic ring containing 3-7 atoms, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl substituted by a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>;
- 20 R<sub>20</sub> and R<sub>21</sub> taken together can form an optionally substituted ring of 3-7 atoms;
- 30 X is N, O, S(O)<sub>n</sub>, C(O), (CR<sub>11</sub>R<sub>12</sub>)<sub>p</sub>, a single bond to R<sub>8</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl, substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, or substituted C<sub>2</sub>-C<sub>6</sub> alkynyl; when X is O, S(O)<sub>n</sub>, C(O), or CR<sub>11</sub>R<sub>12</sub> only R<sub>8</sub> is possible;
- Z is O, S or NR<sub>11</sub>;

m is 0-3;

n is 0-2;

p is 0-4; and

5 the alkyl, cycloalkyl, alkenyl and alkynyl substituents are selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, hydroxy, oxo, cyano, C<sub>1</sub>-C<sub>6</sub> alkoxy, fluoro, C(O)OR<sub>11</sub>, aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, and the aryl substituents are as defined for R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>;

10 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

Preferred substituents when R<sub>20</sub> and R<sub>21</sub> are taken together include 7-aza-bicyclo[2.2.1]heptane and 2-aza-bicyclo[2.2.2]  
15 octane.

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and claims.

When any variable (e.g., aryl, heterocycle, R<sub>1</sub>, etc.) occurs more than one time in any constituent or in formula I, its  
20 definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the  
25 specified number of carbon atoms, e.g., methyl (Me), ethyl (Et), propyl, butyl, pentyl, hexyl, heptyl, octyl, nonanyl, decyl, undecyl, dodecyl, and the isomers thereof such as isopropyl (i-Pr), isobutyl (i-Bu), sec-butyl (s-Bu), tert-butyl (t-Bu), isopentane, isohexane, etc.

The term "aryl" includes phenyl and naphthyl. Preferably,  
30 aryl is phenyl.

The term "halogen" or "halo" is intended to include fluorine, chlorine, bromine and iodine.

The term "heterocycle" or "heterocyclic ring" is defined by all non-aromatic, heterocyclic rings of 3-7 atoms containing 1-3  
35 heteroatoms selected from N, O, and S, such as oxirane, oxetane,

tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, tetrahydropyridine, tetrahydropyrimidine, tetrahydrothiophene, tetrahydrothiopyran, morpholine, hydantoin, valerolactam, pyrrolidinone, and the like.

5           The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment. The heteroaryl group is optionally substituted with up to three  
10 groups.

Heteroaryl includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this are indole, thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, benzimidazole, pyridine, pyrimidine,  
15 pyrazine and triazine.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the  
20 specified amounts.

In addition, it is well known to those skilled in the art that many of the foregoing heterocyclic groups can exist in more than one tautomeric form. It is intended that all such tautomers be included within the ambit of this invention.

25           The optical isomeric forms, that is mixtures of enantiomers, e.g., racemates, or diastereomers as well as individual enantiomers or diastereomers of the instant compound are included. These individual enantiomers are commonly designated according to the optical rotation they effect by the symbols (+) and (-), (L) and (D), (1) and (d) or combinations thereof. These isomers may also be designated  
30 according to their absolute spatial configuration by (S) and (R), which stands for sinister and rectus, respectively.

The individual optical isomers may be prepared using conventional resolution procedures, e.g., treatment with an appropriate  
35 optically active acid, separating the diastereomers and then recovering

the desired isomer. In addition, the individual optical isomers may be prepared by asymmetric synthesis.

Additionally, a given chemical formula or name shall encompass pharmaceutically acceptable addition salts thereof and  
5 solvates thereof, such as hydrates.

The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility and other desirable  
10 properties.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" is intended to include all acceptable salts. Examples of acid salts are hydrochloric, nitric,  
15 sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or prodrug formulations. Depending on the particular functionality of the compound of the present invention,  
20 pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine,  
25 diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethyl-ammonium hydroxide. These salts may be prepared by standard procedures, e.g. by reacting a free acid with a suitable organic or inorganic base, or alternatively by reacting a free base with a suitable  
30 organic or inorganic acid.

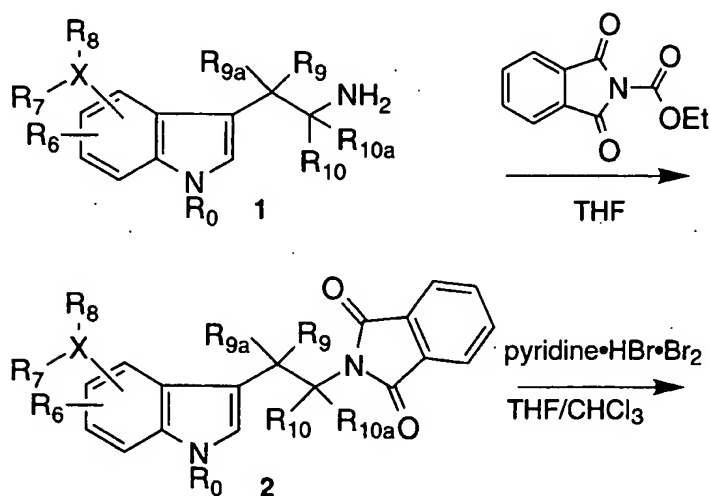
Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed, e.g. methyl, ethyl, butyl, acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis  
35 characteristics for use as sustained release or prodrug formulations.

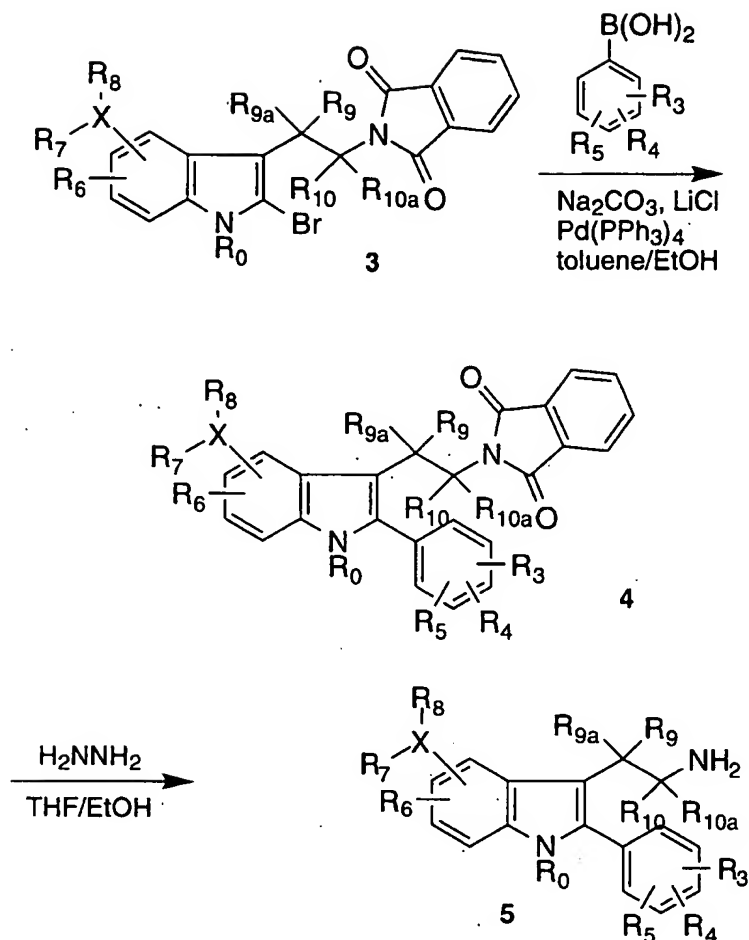


The compounds of the present invention may have chiral centers other than those centers whose stereochemistry is depicted in formula I, and therefore may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers, with all such isomeric forms being included in the present invention as well as mixtures thereof. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

The compounds of the invention are prepared by the following reaction schemes. All substituents are as defined above unless indicated otherwise.

Scheme A



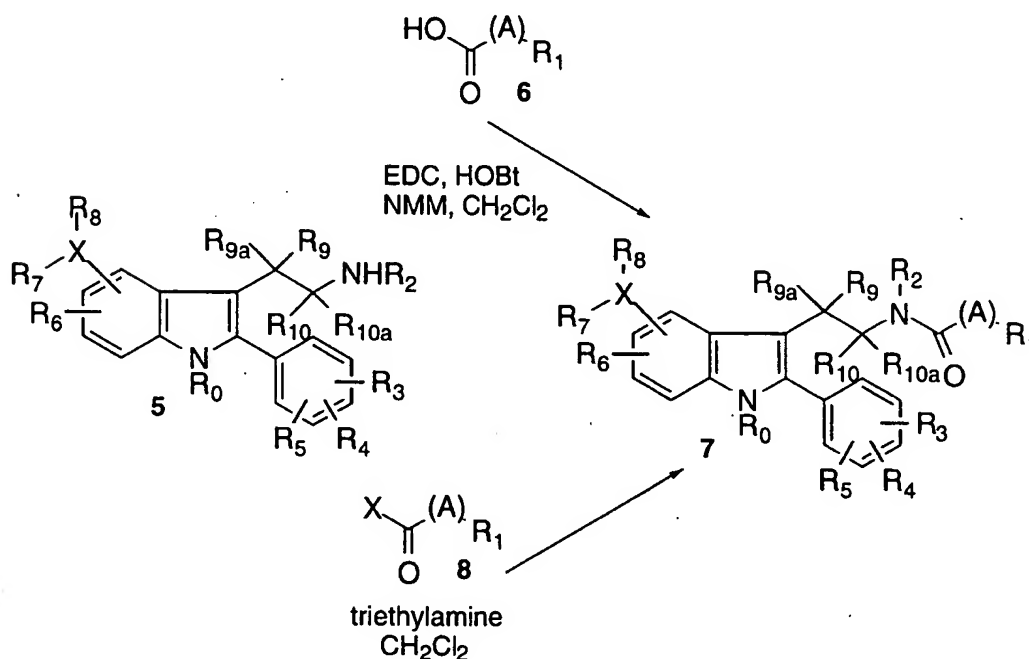


### Reaction Scheme A

- 5 As shown in reaction Scheme A, treatment of tryptamine (1) with *N*-carboxyphthalimide in an inert organic solvent such as tetrahydrofuran at a temperature of 20-65°C, preferably 65°C, for a period of 12-48 hours gives the corresponding *N*-phthalimidotryptamine derivative (2). The *N*-phthalimidotryptamine (2) could be further modified by treatment with a brominating agent such as pyridinium hydrobromide perbromide, pyrrolidone hydrotribromide, or the like in an inert organic solvent such as tetrahydrofuran, methylene chloride, chloroform, or mixtures thereof at 0-25°C for a period of 30 minutes
- 10

- to 4 hours to provide the 2-bromotryptamine (3). Bromide (3) may be reacted with an arylboronic acid (prepared essentially as described in : Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.-H. *Chem. Scr.* **1986**, *26*, 311-314.) with palladium (0) catalysis, a weak base such as aqueous sodium carbonate or the like, and a chloride source such as lithium chloride in an inert solvent like toluene, benzene, ethanol, propanol or mixtures thereof at a temperature of 25°-100°C, preferably 80°C, for a period of 1-6 hours to give the 2-aryltryptamine derivative (4). Finally, the phthalimido group may be removed by treatment of (4) with aqueous hydrazine in an inert solvent such as methanol or ethanol at a temperature of 0°-25°C for a period of 4-24 hours to give tryptamine (5).

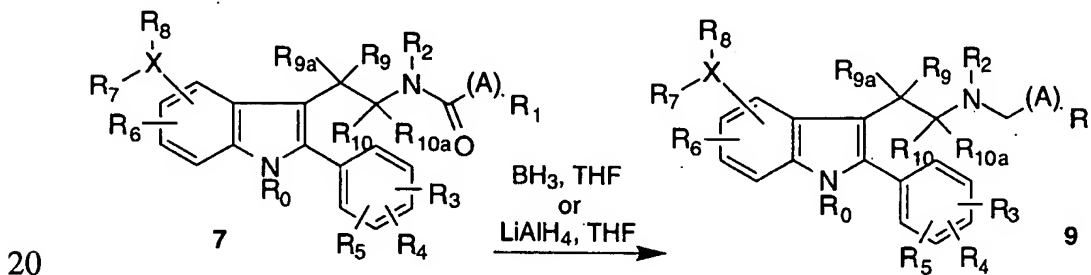
Scheme B



15

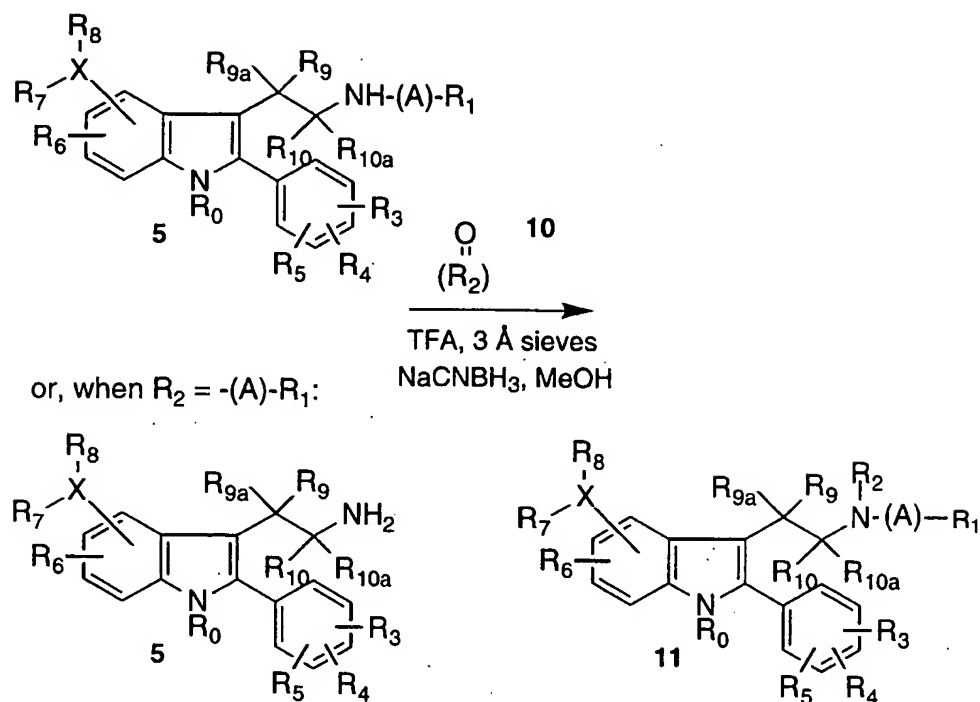
Reaction Scheme B

As shown in reaction Scheme B, the 2-aryltryptamine may be condensed with a carboxylic acid of type (6) using the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or the like with or without 1-hydroxybenzotriazole (HOBt) and a tertiary amine base such as N-methylmorpholine (NMM), triethylamine or the like in an inert organic solvent such as methylene chloride, chloroform, dimethylformamide, or mixtures thereof at or near room temperature for a period of 3-24 hours to provide the corresponding amide derivative (7). Alternatively, 2-aryltryptamine (5) can be treated with an active ester or acid chloride of type (8) in an inert organic solvent such as methylene chloride, chloroform, tetrahydrofuran, diethyl ether, or the like and a tertiary amine base such as triethylamine, diisopropylethylamine, pyridine or the like at a temperature of 0°-25°C for 30 minutes to 4 hours to give (7).

Scheme CReaction Scheme C

As shown in reaction Scheme C, the amide carbonyl of (7) can be reduced by treatment with borane, lithium aluminum hydride, or equivalent hydride sources in an inert organic solvent such as tetrahydrofuran, diethyl ether, 1,4-dioxane or the like at 25°-100°C, preferably 65°C, for a period of 1-8 hours to give the corresponding amine compound (9).

Scheme D

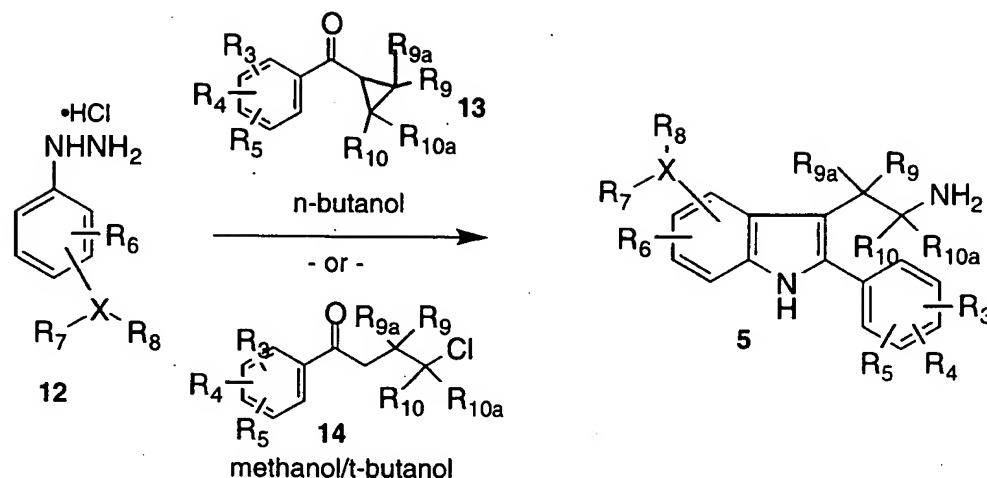


5

Reaction Scheme D

As shown in reaction Scheme D, the 2-aryltryptamine (5) can be modified by treatment with an aldehyde or ketone of type (10) in the presence of a weak acid such as trifluoroacetic acid (TFA), acetic acid or the like, with or without a dessicant such as 3Å molecular sieves or magnesium sulfate, and a hydride source such as sodium borohydride or sodium cyanoborohydride, in an inert organic solvent such as methanol, ethanol, isopropanol, tetrahydrofuran, dichloromethane, chloroform, or mixtures thereof at a temperature of 0°-25°C for a period of 1-12 hours to give the corresponding secondary or tertiary amine derivative (11).

Scheme E

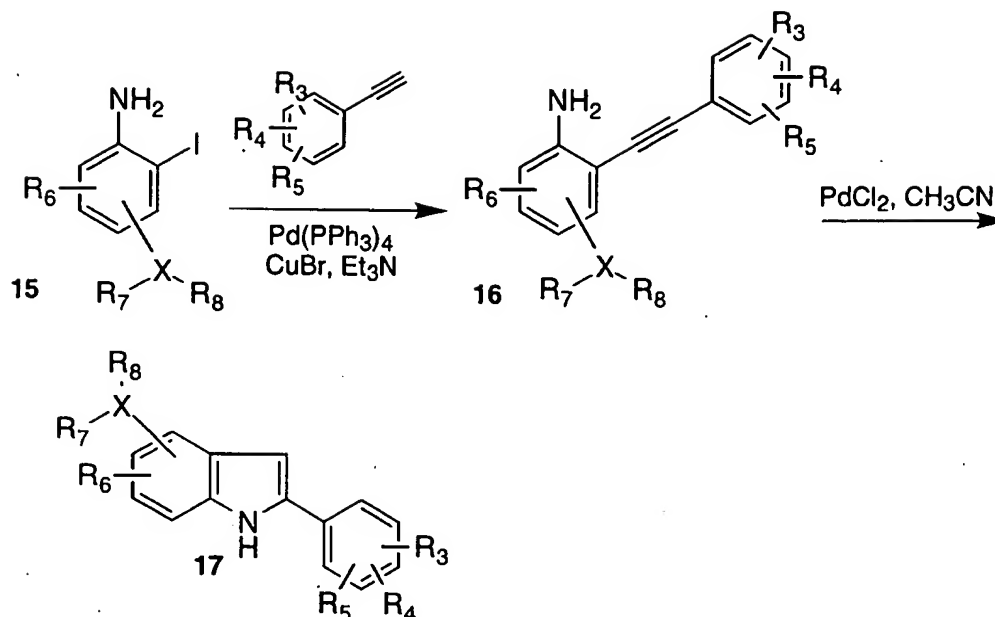


5

Reaction Scheme E

As shown in reaction Scheme E, treatment of an arylhydrazine or arylhydrazine hydrochloride (12) with an arylcyclopropylketone of type (13) in a polar organic solvent such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, preferably n-butanol, at a temperature of 70°-120°C for a period of 8-24 hours gives 2-aryltryptamine (5). Alternatively, when an arylhydrazine or arylhydrazine hydrochloride (12) is treated with an arylbutyl ketone of type (14) containing a leaving group (chloride, bromide, iodide, O-methansulfonate, O-trifluoromethansulfonate, or the like) at the 4-position in a polar solvent such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, or mixtures thereof at room temperature for a period of 30 minutes to 2 hours followed by heating to a temperature of 65°-100°C for 4-24 hours, 2-aryltryptamine (5) is produced.

Scheme F

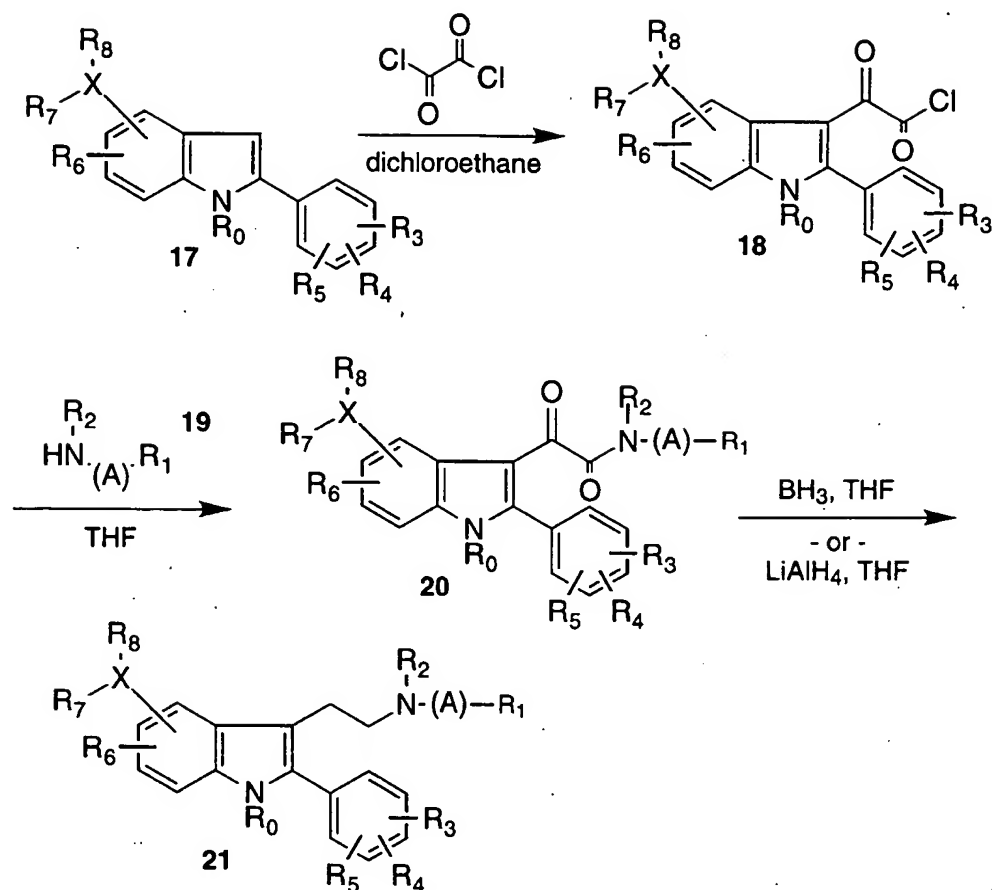


5

Reaction Scheme F

As shown in reaction Scheme F, iodoanilines of type (15) may be reacted with aryl acetylenes, an appropriate palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium, a copper (I) halide such as cuprous bromide in an inert organic solvent such as triethylamine at a temperature of 50°-88°C for a period of 30 minutes to 5 hours to provide the diarylacetylene (16). Acetylene (16) may be further modified by treatment with a palladium (II) catalyst such as palladium (II) chloride or palladium (II) acetate in an inert organic solvent such as acetonitrile at a temperature of 50°- 82°C for a period of 30 minutes to 6 hours to give 2-arylindole (17).

Scheme G

Reaction Scheme G

5 As shown in reaction Scheme G, treatment of 2-arylindole (17) with oxalyl chloride, neat or in an inert organic solvent such as methylene chloride, chloroform, dichloroethane, tetrahydrofuran or the like at a temperature of 25°-65°C for a period of 3-24 hours gives the acylchloride adduct (18). The crude product (18) may be reacted with an amine of type (19) in an inert organic solvent such as diethylether, tetrahydrofuran, methylene chloride, chloroform or the like and an amine base such as triethylamine, diisopropylethylamine or pyridine at a temperature of 0°C-25°C for a period of 30 minutes to 4 hours to provide the amide derivative (20). Amide (20) may be further modified by

10

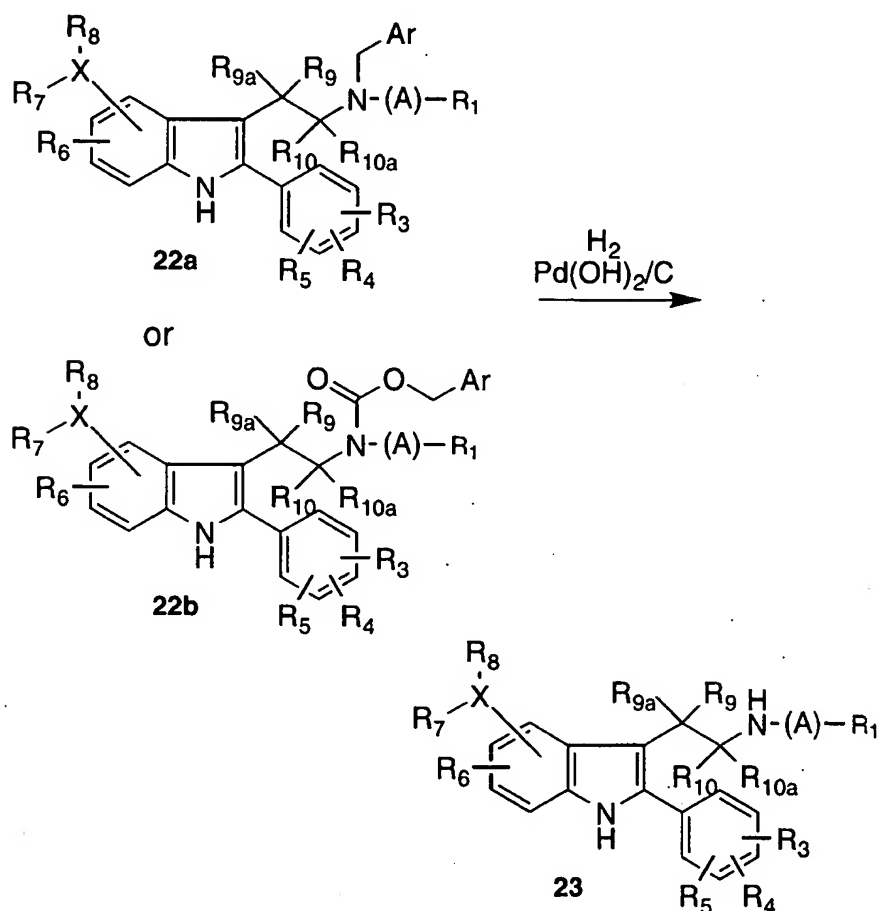
15



treatment with a reducing agent such as borane or lithium aluminum hydride in an inert organic solvent such as tetrahydrofuran at elevated temperatures, preferably reflux, for a period of 1-5 hours to give compound (21).

5

Scheme H



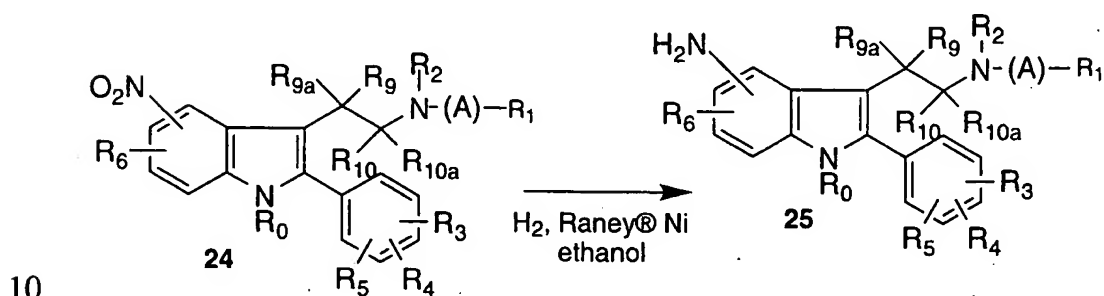
10

Reaction Scheme H

As shown in reaction Scheme H, N-benzyl derivatives of type (22a) or N-benzyloxycarbonyl derivatives of type (22b) may

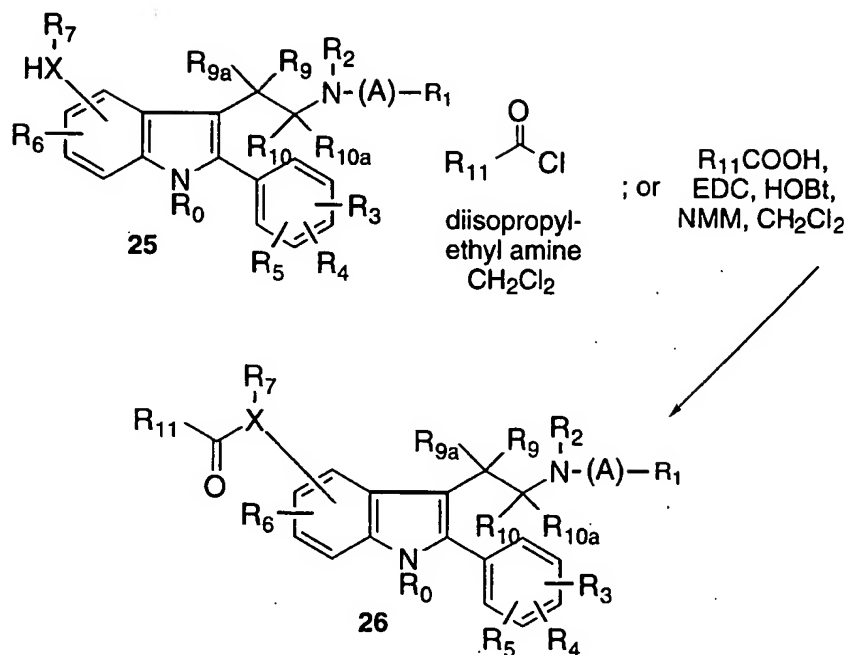
- be reduced to provide the secondary amine analogs (7) by treatment with hydrogen (1 atm) and an appropriate catalyst such as palladium on carbon, palladium hydroxide on carbon, or the like in an inert organic solvent such as tetrahydrofuran, ethyl acetate, methanol, ethanol, or mixtures thereof to which has been added a weak acid such as 30% aqueous acetic acid for a period of 10 minutes to 3 hours or until the aryl group has been removed to give the secondary amine.

Scheme I

Reaction Scheme I

- 15 As shown in reaction Scheme I, treatment of a nitroindole of type (24) with hydrogen (1 atm) and an appropriate catalyst such as Raney® Nickel in an inert organic solvent such as ethanol, methanol, or the like at room temperature for a period of 2-1/2 hours gives the corresponding aminoindole derivative (25).

Scheme J



5

Reaction Scheme J

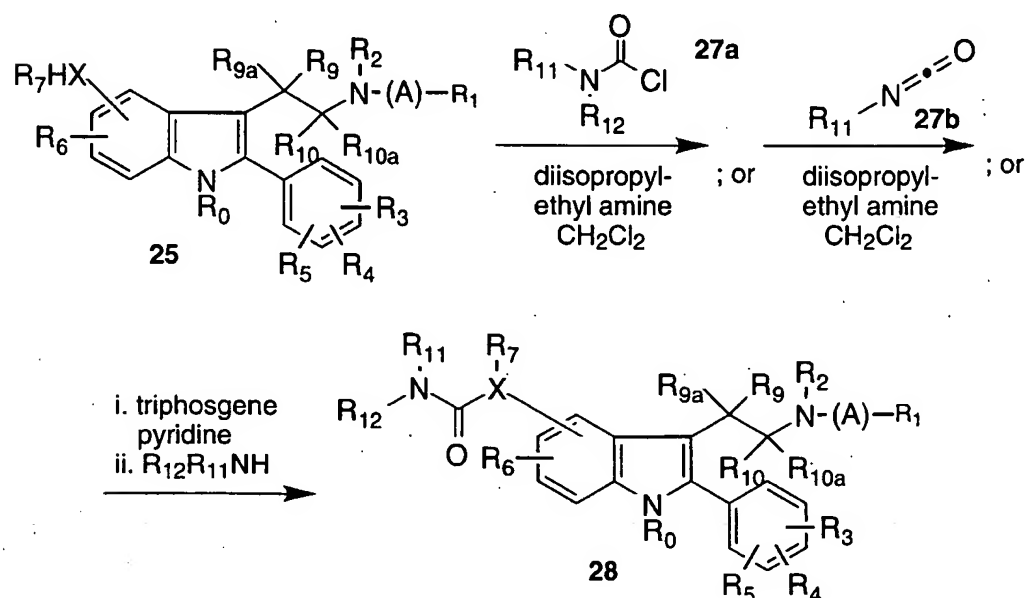
As shown in reaction Scheme J, amino- or hydroxyindole (25) may be modified by acylation under a variety of conditions.

- 10 For example, treatment of (25) with an acid chloride, acid anhydride or active ester and an amine base such as triethylamine, diisopropylethylamine, pyridine, or the like in an inert organic solvent such as methylene chloride, chloroform, tetrahydrofuran, or mixtures thereof at 0°C to room temperature for a period of 1 to 12 hours gives the
- 15 corresponding amide or ester derivatives (26). Alternatively (25) may be coupled with a carboxylic acid by one of the many dehydrating agents commonly employed. For instance, treatment of aminoindole (25) with an appropriate carboxylic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide
- 20 (DCC) or the like with or without 1-hydroxybenzotriazole (HOBT) and a tertiary amine base such as N-methylmorpholine (NMM), triethylamine

or the like in an inert organic solvent such as methylene chloride, chloroform, dimethylformamide, or mixtures thereof at or near room temperature for a period of 3-24 hours provides the corresponding amide or ester derivative (26).

5

Scheme K



10

Reaction Scheme K

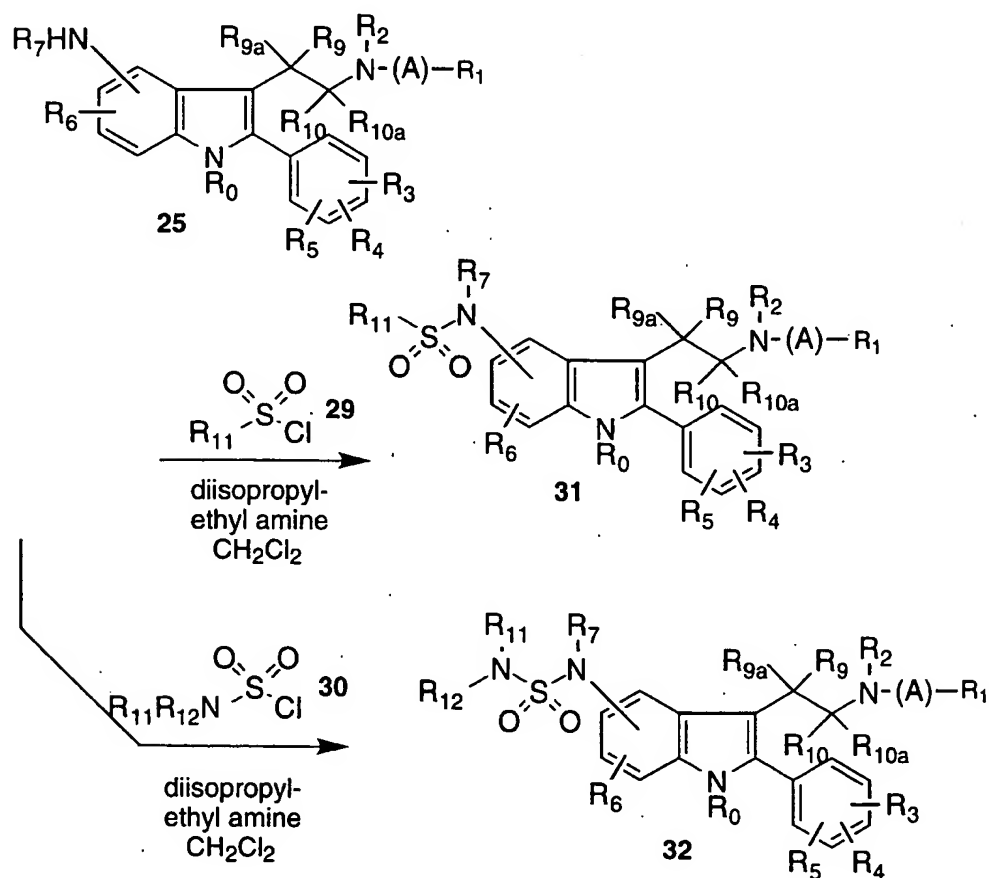
As shown in reaction Scheme K, urea or carbamate derivatives of (25) can be prepared by treatment with a carbamoyl chloride of type (27a), or alternatively with an isocyanate reagent of type (27b), and an amine base such as pyridine, triethylamine, diisopropylethylamine, *N*-methylmorpholine or the like in an inert organic solvent such as methylene chloride, chloroform, dimethylformamide, tetrahydrofuran or mixtures thereof at a temperature of 0°-65°C for a period of 1-72 hours to give (28). Compound (25) can also be modified by treatment with a bis(electrophilic) reagent such as phosgene, triphosgene, 1,1'-carbonyldiimidazole, *N,N'*-disuccinimidyl carbonate, or the like with or without the addition of an amine base such

20

- as pyridine, triethylamine, diisopropylethylamine, *N*-methylmorpholine in an inert solvent such as methylene chloride, chloroform, or the like at a temperature of -20°-0°C for a period of 20 minutes to 2 hours. After this time, the reaction mixture is treated with an appropriate mono- or
- 5 disubstituted amine at -20° to 25°C for a period of 1-5 hours to give the urea or carbamate analog (28).

Scheme L

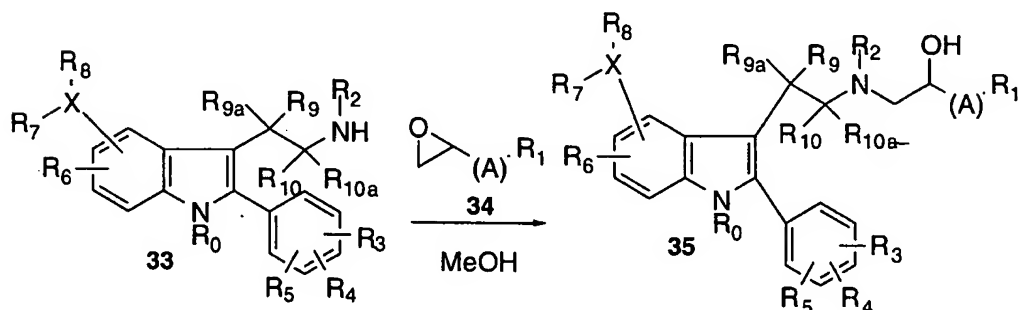
10



Reaction Scheme L

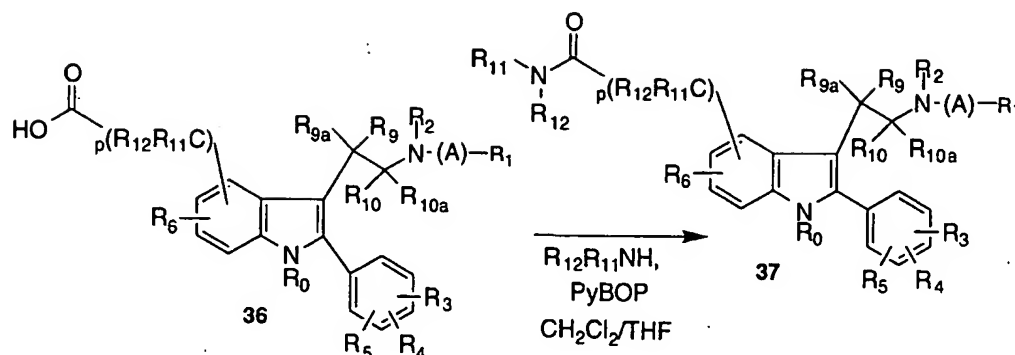
As shown in reaction Scheme L, amine (25) can be modified by treatment with an appropriate sulfonyl chloride of type (29) or sulfamyl chloride of type (30) with an amine base such as pyridine, triethylamine, diisopropylethylamine, *N*-methylmorpholine in an inert solvent such as methylene chloride, chloroform, dichloroethane or the like at a temperature of -20°-25°C for a period of 20 minutes to 2 hours to give the corresponding *N*-sulfonamide (31) or *N*-sulfamylamide (32) derivatives, respectively.

## Scheme M

Reaction Scheme M

As shown in reaction Scheme M, the 2-aryltryptamine (33) can be modified by treatment with an epoxide such as (34) in an inert organic solvent such as methanol, ethanol, isopropanol, butanol, tert-butanol, or mixtures thereof at a temperature of 65°-110°C for a period of 8-20 hours to give the corresponding amino-alcohol derivative (35).

## Scheme N

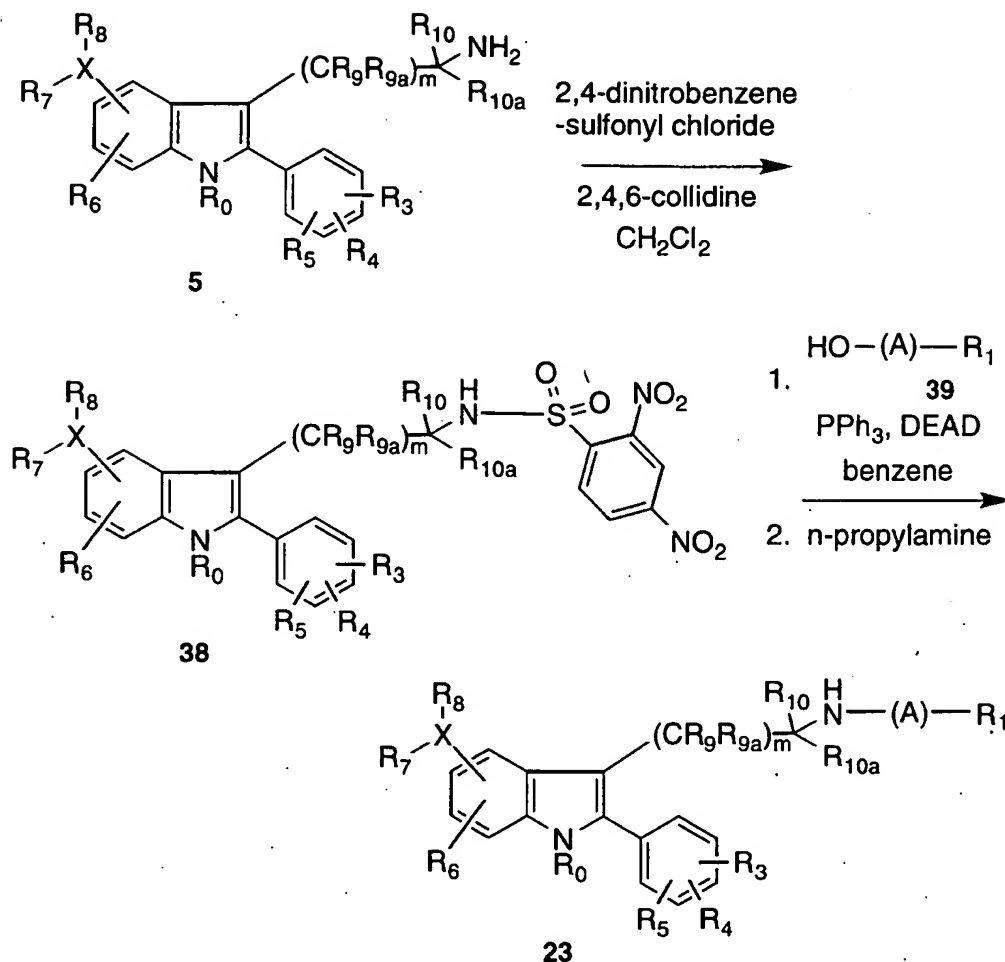


5

Reaction Scheme N

As shown in reaction Scheme N, amide derivatives of an acid-containing indole derivative such as (36) can be prepared by treatment with an appropriate amine (R<sub>12</sub>R<sub>11</sub> NH) and a suitable coupling agent such as benzotriazol-1-yloxy-tris(pyrrolidino) phosphonium hexafluorophosphate (PyBOP), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or the like with or without 1-hydroxybenzotriazole (HOBt) and a tertiary amine base such as N-methylmorpholine (NMM), triethylamine or the like in an inert organic solvent such as methylene chloride, chloroform, tetrahydrofuran, dimethylformamide, or mixtures thereof at or near room temperature for a period of 3 hours to 7 days provides the corresponding amide derivative (37).

## Scheme O



5

Reaction Scheme O

As shown in reaction Scheme O, the tryptamine 5 can be modified by reaction with an arylsulfonyl chloride such as 2-nitrobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride or 2,4-dinitrobenzenesulfonyl chloride and a hindered amine base such as 2,4,6-collidine, 2,6-lutidine or the like in an inert organic solvent such as methylene chloride to provide the corresponding sulfonamide 38. Sulfonamides such as 38 can be further modified by reaction with an alcohol of type 39 in the presence of triphenylphosphine and an



activating agent such as diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate or the like in an inert organic solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the dialkyl-sulfonamide adduct. Removal of the sulfonyl group is accomplished  
5 by treatment with a nucleophilic amine such as n-propylamine or the like in an inert organic solvent such as methylene chloride to give secondary amines of type 23.

The compounds of the present invention are useful in the treatment of various sex-hormone related conditions in men and  
10 women. This utility is manifested in their ability to act as antagonists of the neuropeptide hormone GnRH as demonstrated by activity in the following *in vitro* assays.

Human GnRH receptor binding assay

15 Crude membranes prepared from CHO cells expressing human GnRH receptors were the sources for GnRH receptor. [<sup>125</sup>I]Buserelin (a peptidyl GnRH analog) was used as the radiolabelled ligand. The binding activity was determined as an IC<sub>50</sub> which is the antagonist concentration required to inhibit the specific binding of  
20 [<sup>125</sup>I]buserelin to GnRH receptors by 50%.

Rat pituitary GnRH receptor binding assay:

Crude plasma membranes prepared from rat pituitary tissues were incubated in a Tris.HCl buffer (50 mM, PH. 7.5) containing  
25 bovine serum albumin (.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the desired concentration of a test compound. The assay mixtures were incubated at 4°C for 90-120 minutes followed by rapid filtration and repeated washings through a glass fiber filter. The radioactivity of membrane bound radioligands was determined in a  
30 gamma-counter. From this data, the IC<sub>50</sub> of the radioligand binding to GnRH receptors in the presence of test compound was estimated.

Inhibition of LH release assay:

Active compounds from the GnRH receptor binding assay were further evaluated with an *in vitro* LH release assay to confirm their antagonist activity (blocking GnRH-induced LH release).

5

1. Sample Preparation

The compounds to be assayed were dissolved and diluted in DMSO. The final concentration of DMSO in the incubation medium was 0.5%.

10

2. Assay

The Wistar male rats (150-200 grams) were obtained from Charles River Laboratories (Wilmington, MA). Rats were maintained at a constant temperature (25°C) on a 12-hr light, 12-hr dark cycle. Rat chow and water were available *ad libitum*. The animals were sacrificed by decapitation and pituitary glands were aseptically removed and placed in Hank's Balanced Salt Solution (HBSS) in a 50-mL polypropylene centrifuge tube. The collection tube was centrifuged for 5 min at 250 x g, and HBSS was removed by aspiration. Pituitary glands were transferred to a disposable petri plate and minced with a scalpel. The minced tissue was then transferred to a 50-mL disposable centrifuge tube by suspending the tissue fragments in three successive 10-mL aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase. The cell dispersion was carried out in a water bath at 37°C with gentle stirring for 30 min. At the end of the incubation, the cells were aspirated 20 to 30 times with a pipet and the undigested pituitary fragments were allowed to settle for 3 to 5 min. The suspended cells were removed by aspiration, and then subjected to a 1200 x g centrifugation for 5 min. The cells were then resuspended in Culture medium. The undigested pituitary fragments were treated with 30 mL aliquots of the digestion enzymes as above for a total of 3 digestions with the collagenase/hyaluronidase mixture. The resulting cell suspensions were pooled, counted and diluted to a concentration of  $3 \times 10^5$  cells/ml, and 1.0 ml of this suspension was placed in each well of a 24-well tray (Costar, Cambridge, MA). Cells were maintained in a humidified 5% CO<sub>2</sub>-95% air

35

atmosphere at 37°C for 3 to 4 days. The culture medium consisted of DMEM containing 0.37% NaHCO<sub>3</sub>, 10% horse serum, 2.5% fetal bovine serum, 1% non-essential amino acids, 1% glutamine, and 0.1% gentamycin. On the day of an experiment, cells were washed three  
5 times 1 1/2 hrs prior to and two more times immediately before the start of the experiment with DMEM containing 0.37% NaHCO<sub>3</sub>, 10% horse serum, 2.5% fetal bovine serum, 1% non-essential amino acids(100X), 1% glutamine(100X), 1% Penicillin/Streptomycin(10,000 Units of Penicillin and 10,000 micrograms of Streptomycin per ml), and 25 mM  
10 HEPES, pH 7.4. LH release was initiated by adding 1 ml of fresh medium containing test compounds in the presence of 2 nM GnRH to each well in duplicate. Incubation was carried out at 37°C for 3 hr. After incubation, medium was removed and centrifuged at 2,000 x g for 15 min to remove any cellular material. The supernatant fluid was  
15 removed and assayed for LH content with a double antibody RIA procedure using materials obtained from Dr. A. F. Parlow (Harbor-UCLA Medical Center, Torrance, CA).

The compounds of formula I are useful in a number of areas affected by GnRH. They may be useful in sex-hormone related  
20 conditions, sex-hormone dependent cancers, benign prostatic hypertrophy or myoma of the uterus. Sex-hormone dependent cancers which may benefit from the administration of the compounds of this invention include prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenomas. Other sex-hormone dependent conditions  
25 which may benefit from the administration of the compounds of this invention include endometriosis, polycystic ovarian disease, uterine fibroids and precocious puberty. The compounds may also be used in combination with an angiotensin-converting enzyme inhibitor such as Enalapril or Captopril, an angiotensin II-receptor antagonist such as  
30 Losartan or a renin inhibitor for the treatment of uterine fibroids.

The compounds of the invention may also be useful for controlling pregnancy, as a contraceptive in both men and women, for *in vitro* fertilization, in the treatment of premenstrual syndrome, in the treatment of lupus erythematosus, in the treatment of hirsutism, in the

treatment of irritable bowel syndrome and for the treatment of sleep disorders such as sleep apnea.

A further use of the compounds of this invention is as an adjunct to growth hormone therapy in growth hormone deficient children. The compounds may be administered with growth hormone or a compound which increases the endogenous production or release of growth hormone. Certain compounds have been developed which stimulate the release of endogenous growth hormone. Peptides which are known to stimulate the release of endogenous growth hormone include growth hormone releasing hormone, the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890, PCT Patent Pub. No. WO 89/07110, and PCT Patent Pub. No. WO 89/07111) and GHRP-2 (described in PCT Patent Pub. No. WO 93/04081), as well as hexarelin (J. Endocrinol Invest., 15 (Suppl 4), 45 (1992)). Other compounds which stimulate the release of endogenous growth hormone are disclosed, for example, in the following: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

Representative preferred growth hormone secretagogues employed in the present combination include the following:

- 1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;  
5
- 2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 10 3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 15 4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide;  
20
- 6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide;
- 25 7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate;
- 30 8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethoxy)ethyl]-2-amino-2-methylpropanamide;
- 35 9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide;

- 10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;
- 5
- 11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide;
- 10
- 12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide;
- 15
- 13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide;
- 20
- 14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 25
- 15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 30
- 16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

The compounds of the invention may also be used in combination with bisphosphonates (bisphosphonic acids) and other agents, such as growth hormone secretagogues, e.g. MK-0677, for the treatment and the prevention of disturbances of calcium, phosphate and bone metabolism, in particular, for the prevention of bone loss during therapy with the GnRH antagonist, and in combination with estrogens, progesterones and or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with the GnRH antagonist.

10 Bisphosphonates (bisphosphonic acids) are known to inhibit bone resorption and are useful for the treatment of bone lithiasis as disclosed in U.S. Patent 4,621,077 to Rosini, et al.

The literature discloses a variety of bisphosphonic acids which are useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Patent No. 3,251,907; U.S. Patent No. 3,422,137; U.S. Patent No. 3,584,125; U.S. Patent No. 3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,578,376; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,761,406; U.S. Patent No. 4,922,007; U.S. Patent No. 4,942,157; U.S. Patent No. 5,227,506; U.S. Patent No. 5,270,365; EPO Patent Pub. No. 0,252,504; and J. Org. Chem., 36, 3843 (1971).

25 The preparation of bisphosphonic acids and halo-bisphosphonic acids is well known in the art. Representative examples may be found in the above mentioned references which disclose the compounds as being useful for the treatment of disturbances of calcium or phosphate metabolism, in particular, as inhibitors of bone resorption.

30 Preferred bisphosphonates are selected from the group of the following compounds: alendronic acid, etidrononic acid, clodronic acid, pamidronic acid, tiludronic acid, risedronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid, and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid;

or any pharmaceutically acceptable salt thereof. A particularly preferred bisphosphonate is alendronic acid (alendronate), or a pharmaceutically acceptable salt thereof. An especially preferred bisphosphonate is alendronate sodium, including alendronate sodium trihydrate. Alendronate sodium has received regulatory approval for marketing in the United States under the trademark FOSAMAX®.

Additionally, a compound of the present invention may be co-administered with a 5 $\alpha$ -reductase 2 inhibitor, such as finasteride or epristeride; a 5 $\alpha$ -reductase 1 inhibitor such as 4,7b-dimethyl-4-aza-5 $\alpha$ -cholestan-3-one, 3-oxo-4-aza-4,7b-dimethyl-16b-(4-chlorophenoxy)-5 $\alpha$ -androstane, and 3-oxo-4-aza-4,7b-dimethyl-16b-(phenoxy)-5 $\alpha$ -androstane as disclosed in WO 93/23420 and WO 95/11254; dual inhibitors of 5 $\alpha$ -reductase 1 and 5 $\alpha$ -reductase 2 such as 3-oxo-4-aza-17b-(2,5-trifluoromethylphenyl-carbamoyl)-5 $\alpha$ -androstane as disclosed in WO 95/07927; antiandrogens such as flutamide, casodex and cyproterone acetate, and alpha-1 blockers such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin.

Further, a compound of the present invention may be used in combination with growth hormone, growth hormone releasing hormone or growth hormone secretagogues, to delay puberty in growth hormone deficient children, which will allow them to continue to gain height before fusion of the epiphyses and cessation of growth at puberty.

Further, a compound of the present invention may be used in combination or co-administered with a compound having luteinizing hormone releasing activity such as a peptide or natural hormone or analog thereof. Such peptide compounds include leuporelin, gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterlin and recirelin.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agent.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets,



troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical

- 5 compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically
- 10 acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or
- 15 acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl
- 20 monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

- Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert
- 25 solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

- Aqueous suspensions contain the active material in
- 30 admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring

phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example

polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such  
5 formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable  
10 dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water,  
15 Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

20 Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release  
25 the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. For purposes of this application, topical application shall include mouth washes and gargles.

30 The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage  
35 administration will, of course, be continuous rather than intermittent

throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of structural formula I useful in the method of the present invention range from 0.01 to 1000 mg per adult human per day. Most preferably, dosages range from 0.1 to 500 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in dividend doses of two, three or four times daily.

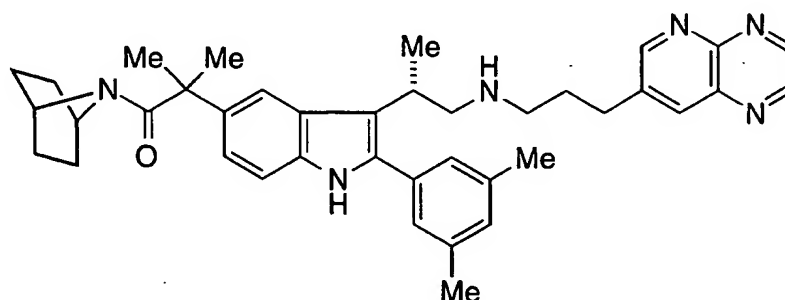
The amount of active ingredient that may be combined

with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate the preparation of some of the compounds of the invention and are not to be construed as limiting the invention disclosed herein.

#### EXAMPLE 1.1



(S)-1-(7-aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethylphenyl)-3-[1-methyl-2-(3-pyridylpyrazin-7-yl)propylamino)-ethyl]-1H-indol-5-yl}-2-methylpropan-1-one

Step 1.1A (S)-2-[3-(2-amino-1-methylethyl)-7-bromo-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropionic acid ethyl ester

A mixture of 0.107 g of ethyl 2-(3-bromo-4-hydrazinophenyl)-2-methylpropionate, 0.066 g of (R)-4-chloro-1-(3,5-dimethylphenyl)-3-methylbutan-1-one, and 2.0 mL of *tert*-butanol was stirred at reflux under nitrogen for 16 hours. The cooled solution was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and a 10% aqueous sodium thiosulfate solution. The organic phase was washed

with water and brine, then dried over sodium sulfate, and filtered. The residue from concentration of the filtrate *in vacuo* was purified by flash chromatography on silica gel (chloroform:

5 methanol:ammonium hydroxide, 95:5:1) to give the title compound (53 mg).

Step 1.1B (S)-2-[3-(2-amino-1-methylethyl)-2-(3,5-dimethylphenyl)-  
1H-indol-5-yl]-2-methylpropionic acid ethyl ester

To a solution of (S)-2-[3-(2-amino-1-methylethyl)-7-bromo-2-  
10 (3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropionic acid ethyl ester (79 mg in 1 mL methanol) was added 8 mg of 10% palladium on carbon catalyst. The reaction flask was fitted with a hydrogen balloon, evacuated and recharged with hydrogen (3 times) and stirred at room temperature. After 7 hours the reaction was flushed with nitrogen,  
15 filtered over diatomaceous earth, concentrated *in vacuo* and purified by flash chromatography on silica gel (chloroform:methanol, 92:8) to provide the title compound (68 mg).

Step 1.1C (S)-2-[3-(2-*tert*-butoxycarbonylamino-1-methylethyl)-2-  
20 (3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropionic  
acid ethyl ester

To a solution of (S)-2-[3-(2-amino-1-methylethyl)-2-(3,5-  
dimethylphenyl)-1H-indol-5-yl]-2-methylpropionic acid ethyl ester (2.13 g in 30 mL tetrahydrofuran) at 0°C was added a solution of di-*tert*-butyl  
25 dicarbonate (1.9 g in 6 mL tetrahydrofuran) followed by potassium carbonate (1.2 g in 5 mL water) and the resulting suspension stirred vigorously at 0°C. After 20 minutes, the reaction was quenched by the addition of excess saturated aqueous ammonium chloride and the mixture extracted with ethyl acetate. The organic portion was dried over  
30 sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane:methylene chloride:ethyl acetate, 7.5:7.5:1) to give the title compound (2.52 g).

Step 1.1D (S)-2-[3-(2-*tert*-butoxycarbonylamino-1-methylethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropionic acid

5 To a stirred solution of (S)-2-[3-(2-*tert*-butoxycarbonylamino-1-methylethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropionic acid ethyl ester (2.5 g in 80 mL methanol) was added 26 mL of 2.0N potassium hydroxide and the mixture heated to 94°C on an oil bath. After 14 hours the mixture was cooled to 0 °C, acidified to pH5 and extracted with ethyl acetate. The organic layer was washed with  
10 saturated ammonium chloride, dried over sodium sulfate and concentrated *in vacuo* to give the crude title compound (2.4 g).

Step 1.1E (S)-{2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]-propyl}-carbamic acid *tert*-butyl ester

15 To a stirred solution of (S)-2-[3-(2-*tert*-butoxycarbonylamino-1-methylethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropionic acid (2.5 g in 25 mL dry methylene chloride) at 0 °C was added 1-hydroxybenzotriazole (1.0 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.24 g) and the reagents allowed to mix  
20 for 1 hour. At this time a solution of 7-aza-bicyclo[2.2.1]heptane hydrochloride (1.44 g) was added followed by 1.5 mL triethylamine and the reaction stirred at room temperature. After 21 hours, the mixture was concentrated *in vacuo* and purified by flash chromatography on  
25 silica gel (hexane:ethyl acetate, 1:1) to give the title compound (2.6 g).

Step 1.1F (S)-2-[3-(2-amino-1-methylethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-methylpropan-1-one

30 To a solution of (S)-{2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]-propyl}-carbamic acid *tert*-butyl ester (2.6 g in 90 mL methylene chloride) at 0°C was added 5.2 mL anisole followed by 37 mL trifluoroacetic acid and the mixture stirred at 0°C. After 2 hours, the mixture was  
35 concentrated *in vacuo* and the residual acid removed by azeotrope with

toluene. Purification by flash chromatography on silica gel (methylene chloride:methanol:ammonium hydroxide, 90:7:1) gave the title compound (2.1 g).

- 5    Step 1.1G    (S)-1-(7-aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethylphenyl)-3-[1-methyl-2-(3-pyrido[2,3-*b*]pyrazin-7-yl-propylamino)-ethyl]-1*H*-indol-5-yl}-2-methylpropan-1-one  
To a solution of (S)-2-[3-(2-amino-1-methylethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-methylpropan-1-one (120 mg in 8 mL dry chloroform) at 0°C was added 194 mg magnesium sulfate followed by 51 mg 3-pyrido[2,3-*b*]pyrazin-7-yl-propionaldehyde and the mixture stirred at low temperature. After 1 hour, a solution of sodium cyanoborohydride (34 mg in 0.7 mL methanol) was added followed by 0.25 mL of a solution of acetic acid in methanol (1:9) and the reaction allowed to warm to room temperature. After 1 hour, the reaction was quenched by the addition of saturated sodium bicarbonate and the mixture extracted with ethyl acetate. The organic portion was washed with saturated aqueous sodium bicarbonate and then dried over sodium sulfate. Purification of the concentrate by flash chromatography on silica gel (ethyl acetate; then methylene chloride:methanol:ammonium hydroxide, 94:5:1) gave the title compound (12 mg).

## 25                    PREPARATION OF SYNTHETIC INTERMEDIATES

### Ethyl 2-(3-bromo-4-hydrazinophenyl)-2-methylpropionate

- Step A:    Ethyl (+/-)-2-(4-nitrophenyl)propionate  
30            To a solution of 9.76 g (50 mmol) of (+/-)-2-(4-nitrophenyl)propionic acid in 150 mL of absolute ethanol was added 3.0 mL of concentrated sulfuric acid. The resulting solution was stirred at reflux under nitrogen. After 6 hours, the solution was cooled and stirred vigorously as 250 mL of saturated aqueous sodium bicarbonate solution was added gradually. The mixture was then partitioned
- 35



between 750 mL of ethyl acetate and 500 mL of water. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate solution and then with 100 mL of saturated aqueous sodium chloride solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 10.86 g (97%) of an oil; homogeneous by TLC in 9:1 hexane-ethyl acetate. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) was consistent with the assigned structure.

Step B: Ethyl 2-methyl-2-(4-nitrophenyl)propionate

10 A suspension of 924 mg (23 mmol) of sodium hydride (60% in oil) in 21 mL of dry *N,N*-dimethylformamide was stirred under nitrogen in an ice bath as a solution of 4.68 g (21 mmol) of ethyl (+/-)-2-(4-nitrophenyl)propionate in 20.5 mL of dry *N,N*-dimethylformamide was added gradually over about 10 minutes. An intense violet color developed during the addition. The mixture was then allowed to warm to room temperature. After about 1 hour, the mixture was again cooled in an ice bath as a solution of 1.44 mL (3.28 g; 23 mmol) of methyl iodide in 5 mL of dry *N,N*-dimethylformamide was added dropwise by syringe over about 10 minutes, while maintaining the internal temperature at 10-15 °C.

20 The mixture was allowed to warm to room temperature, and the color changed to brown. After 1 hour, an additional 187 mL (426 mg, 3 mmol) of iodomethane was added. By the next day, the mixture consisted of a suspension of some grayish solid in a golden liquid. It was stirred vigorously and quenched by gradual addition of 10 mL of 5% aqueous potassium bisulfate solution. The mixture was partitioned between 400 mL of diethyl ether and 400 mL of water. The organic layer was washed with an additional 3 x 400 mL of water and then with 50 mL of saturated aqueous sodium chloride solution. The organic phase was then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (elution with 19:1 hexane-ethyl acetate) yielded 4.31 g (87%) of an oil; homogeneous by TLC in 9:1 hexane-ethyl acetate. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) was consistent with the assigned structure.

Step C: Ethyl 2-(4-aminophenyl)-2-methylpropionate

A mixture of 4.27 g (18 mmol) of ethyl 2-methyl-2-(4-nitrophenyl)propionate, 200 mg of 10% palladium on carbon, and 120 mL of absolute ethanol was shaken with hydrogen (initial hydrogen  
5 pressure 47 psig) in a pressure vessel for 2 hours. The catalyst was removed by filtration through Celite under nitrogen, and the filter cake was washed with additional ethanol. Concentration of the filtrate *in vacuo* at up to 50°C gave 3.74 g (100%) of an oil; homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>) was consistent with the  
10 assigned structure. Mass spectrum (ESI): *m/e* = 208 (M + H).

Step D: Ethyl 2-(4-amino-3-bromophenyl)-2-methylpropionate

To a solution of ethyl 2-(4-aminophenyl)-2-methylpropionate (4.74 g in 40 mL dry methylene chloride) at 0°C was added 4.08 g of *N*-  
15 bromosuccinimide and the mixture stirred at low temperature. After 1 hour, the mixture was warmed to room temperature and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (hexane:ethyl acetate, 9:1; then 8:2) gave the title compound, 5.46 g.

20 Step E: Ethyl 2-(3-bromo-4-hydrazinophenyl)-2-methylpropionate

A solution of 0.091 g of ethyl 2-(4-amino-3-bromophenyl)-2-methylpropionate in 0.32 mL of concentrated hydrochloric acid was stirred at -10 to -5°C in an ice-acetone bath as a solution of 0.023 g of sodium nitrite in 0.20 mL of water was added dropwise over about 15  
25 minutes. Stirring was continued at this temperature for an additional 30 minutes. Next, the supernatant was removed by syringe and added dropwise over 10 minutes to a solution of 0.36 g of stannous chloride dihydrate in 0.25 mL of concentrated hydrochloric acid stirred under nitrogen in an ice-acetone bath. The addition was carried out at such  
30 a rate that the internal temperature remained at about -5°C. A gummy material separated during the addition. After completion of the addition, stirring was continued at -10 to -5°C for 1 hour. The mixture was then diluted with 60 mL ethyl acetate and washed with sodium carbonate. The organic layer was washed with water and brine then

dried over magnesium sulfate. Concentration in vacuo gave the crude title compound.

(R)-4-Chloro-1-(3,5-dimethylphenyl)-3-methylbutan-1-one

5

Step AA: (R)-4-hydroxy-3-methylbutyronitrile

To a solution of (S)-3-bromo-2-methyl-propan-1-ol (5.83g in 25 mL dry *N,N*-dimethylformamide) was added 9.33g sodium cyanide and the mixture heated to 80°C on an oil bath. After 4 hours, the mixture  
10 was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organics were washed with water then brine. Concentration *in vacuo* gave the desired crude product (2.74g).

Step BB: (R)-4-methyldihydrofuran-2-one

To a solution of (R)-4-hydroxy-3-methyl-butyronitrile (2.73g in 39 mL ethanol) was added a solution of sodium hydroxide (1.64g in 13 mL water) and the mixture heated to reflux on an oil bath. After 7 hours, the mixture was cooled and made acidic by the addition of 2N  
15 hydrochloric acid. The organics were removed in vacuo and the mixture then extracted with 90 mL benzene. The organics were washed with brine and transferred to a reaction flask fitted with a Dean-Stark trap. *p*-Toluenesulfonic acid (100 mg) was added and the mixture heated to reflux on an oil bath. After 3 hours, the benzene and product (138 °C)  
20 were collected by distillation under reduced pressure (1.79g).

25

Step CC: (R)-3-(3,5-dimethylbenzoyl)-4-methyldihydrofuran-2-one

To a solution of (R)-4-methyldihydrofuran-2-one (1.68 g in 40 mL dioxane) were added 5.51g 3,5-dimethylbenzoic acid methyl ester followed by 1.82g sodium hydroxide and the mixture heated to  
30 reflux on an oil bath. After 3 hours, the mixture was cooled to room temperature and the pH neutralized by the addition of 0.5N hydrochloric acid. The mixture was then extracted with ethyl acetate and the organic portion washed with brine and dried over sodium sulfate. Purification of the concentrate by flash chromatography on silica gel  
35 (hexane:ethyl acetate, 9:1) gave the title compound (2.42g).

Step DD: (R)-4-chloro-1-(3,5-dimethylphenyl)-3-methylbutan-1-one

To a solution of (R)-3-(3,5-dimethylbenzoyl)-4-methyldihydrofuran-2-one (2.42g in 15 mL dioxane) was added 15 mL conc. hydrochloric acid and the mixture heated to reflux on an oil bath. After one hour, the reaction was poured into cold, saturated aqueous sodium bicarbonate. Additional solid sodium bicarbonate was added until all acid was neutralized. This was then extracted with ethyl acetate, washed with brine. Concentration in vacuo provided the title compound (2.12g).

3-Pyrido[2,3-b]pyrazin-7-yl-propionaldehyde

Step AAA: 7-(3,3-diethoxypropyl)-pyrido[2,3-b]pyrazine

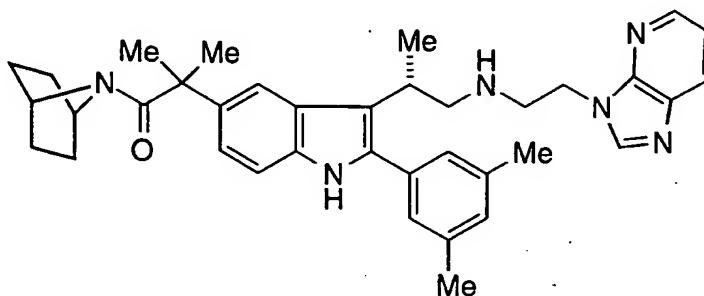
To a solution of 9-BBN (10.2 mL of a 0.5M solution in tetrahydrofuran) at 0°C was added dropwise 0.77 mL of acrolein diethyl acetal and the mixture allowed to warm slowly to room temperature. After 15 hours, the mixture was diluted with 12 mL dry tetrahydrofuran followed by the sequential addition of potassium phosphate (1.6 g), palladium(1,1'-bis(diphenylphosphino)ferrocenyl) dichloride (160 mg) and 7-bromo-pyrido[2,3-b]pyrazine (924 mg) and then heated to reflux on an oil bath. After 5 hours, the mixture was cooled to 0°C, diluted with 15 mL benzene and the excess reagents quenched by the addition of 2N sodium hydroxide (3.5 mL) and 30% hydrogen peroxide (2.5 mL). The mixture then extracted with ethyl acetate, washed with brine and the concentrate purified by flash chromatography on silica gel (ethyl acetate:hexane, 1:4; then 1:1; then 4:1) to give the title compound (1.2 g).

Step BBB: 3-pyrido[2,3-b]pyrazin-7-yl-propionaldehyde

To a solution of 7-(3,3-diethoxypropyl)-pyrido[2,3-b]pyrazine (522 mg in 20 mL chloroform) at 0°C was added 20 mL of 50% aqueous trifluoroacetic acid and the mixture allowed to warm slowly to room temperature. After 30 minutes, the mixture was diluted with methylene chloride and the reaction quenched by the cautious addition of saturated sodium bicarbonate. The organics were concentrated in vacuo and

purified by flash chromatography on silica gel (ethyl acetate:hexane, 1:1; then methylene chloride:methanol, 95:5) to give the title compound (0.214 g).

5

EXAMPLE 1.2

10

(S)-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-[2-(3,5-dimethylphenyl)-  
3-[2-(2-imidazo[4,5-b]pyridin-3-yl-ethylamino)-1-  
methylethyl]-1H-indol-5-yl]-2-methylpropan-1-one

15

Step 1.2A (S)-N-{2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-  
 dimethyl2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1H-indol  
 -3-yl]-propyl]-2,4-dinitrobenzenesulfonamide

20

To a solution of (S)-2-[3-(2-amino-1-methylethyl)-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-methylpropan-1-one (1.1g in 15 mL dry methylene chloride) at 0°C was added 1.3 mL of 2,4,6-collidine followed by 1.3g of 2,4-dinitrobenzenesulfonyl chloride and the mixture warmed slowly to room temperature. After 20 hours, the mixture was diluted with ethyl acetate, washed with brine and the organics concentrated *in vacuo*. Purification by flash chromatography on silica gel (ethyl acetate:hexane, 1:4; then 2:3; then 3:2; then 4:1) gave the title compound (1.57g).

25

Step 1.2B (S)-N-{2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-  
 dimethyl2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1H-  
 indol-3-yl]-propyl]-N-(2-imidazo[4,5-b]pyridin-  
 3-yl-ethyl)-2,4-dinitrobenzenesulfonamide

To a solution of (S)-N-[2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl 2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1H-indol-3-yl]-propyl]-2,4-dinitrobenzenesulfonamide (0.415g in 6 mL benzene) was added 0.20g 2-imidazo[4,5-b]pyridin-3-yl-ethanol followed by 0.32g triphenylphosphine and 0.189mL of diethyl azodicarboxylate added dropwise. After 2 hours, the mixture was concentrated and the crude reaction product purified by flash chromatography on silica gel (methylene chloride:methanol, 98:2; then 95:5) to give the title compound (1.51g).

10

Step 1.2C (S)-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-[2-(3,5-dimethylphenyl)-3-[2-(2-imidazo[4,5-b]pyridin-3-yl-ethylamino)-1-methylethyl]-1H-indol-5-yl]-2-methylpropan-1-one

15

To a solution of (S)-N-[2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl 2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1H-indol-3-yl]-propyl]-N-(2-imidazo[4,5-b]pyridin-3-yl-ethyl)-2,4-dinitrobenzenesulfonamide (1.5g in 15 mL dry methylene chloride) was added 1.5mL of n-propylamine and the mixture stirred at room temperature. After 30 minutes the volatiles were removed *in vacuo* and the concentrate purified by flash chromatography on silica gel (ethyl acetate:hexane 1:1; then 4:1; then methylene chloride:methanol: ammonium hydroxide, 95:4:1) to give the title compound (0.804g).

25

### PREPARATION OF SYNTHETIC INTERMEDIATES

#### 2-imidazo[4,5-b]pyridin-3-yl-ethanol

30 Step A 3H-imidazo[4,5-b]pyridine

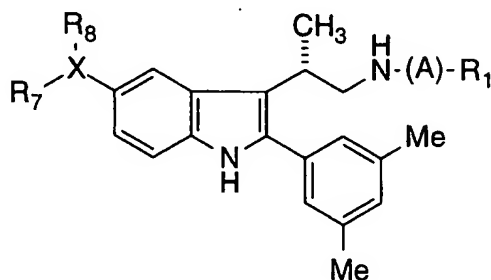
A solution of 2,3-diaminopyridine (2.2g in 20mL triethyl orthoformate) was heated to reflux on an oil bath. After 16 hours, the mixture was cooled and the volatiles removed *in vacuo*. Purification of the concentrate by flash chromatography on silica gel (ethyl acetate;

hexane 4:1; then methylene chloride:methanol: ammonium hydroxide, 94:5:1) gave the title compound (2.04g).

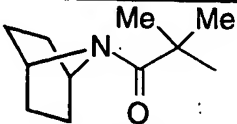
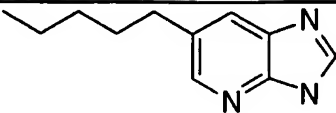
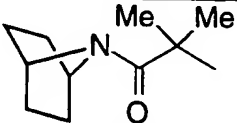
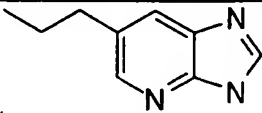
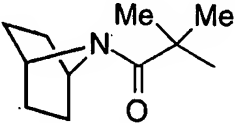
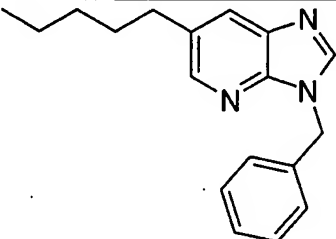
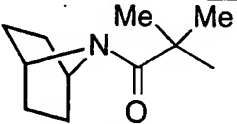
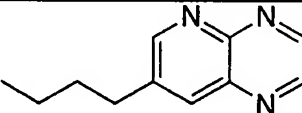
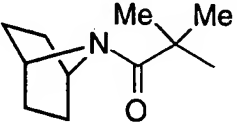
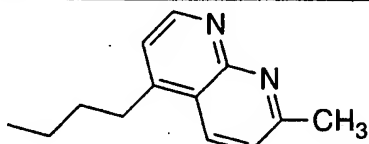
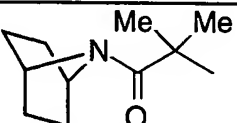
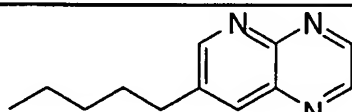
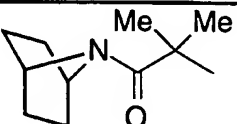
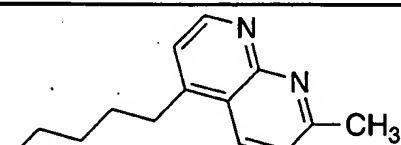
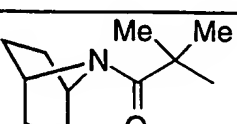
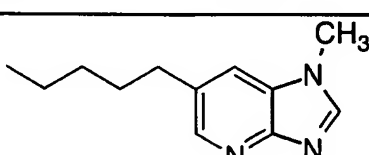
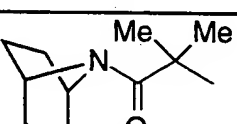
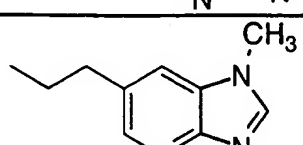
Step B 2-imidazo[4,5-b]pyridin-3-yl-ethanol

- 5 To a solution of 3H-imidazo[4,5-b]pyridine (0.60g in 50 mL benzene) was added 1.4mL ethylene glycol followed by 2.6g triphenylphosphine and 1.5mL of diethyl azodicarboxylate added dropwise. After 1 hour, the mixture was concentrated and the crude reaction product purified by flash chromatography on silica gel  
10 (methylene chloride:methanol, 97:3; then 90:10; then methylene chloride:methanol: ammonium hydroxide, 94:5:1) to give the title compound.

- Following a procedure similar to that described above, the  
15 following compounds were prepared:

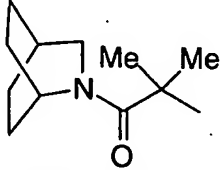
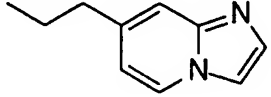
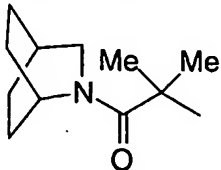
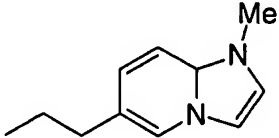
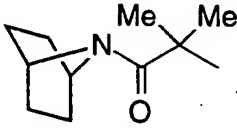
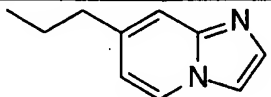
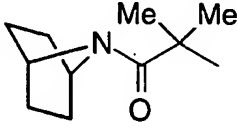
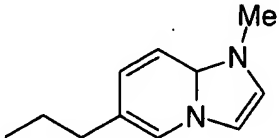


Example #	X-R <sub>7</sub> ,R <sub>8</sub>	-(A)-R <sub>1</sub>	
1A			
1B			

1C			
1D			
1E			
1F		bis 	
1G			
1H			
1I			
1J			
1K			

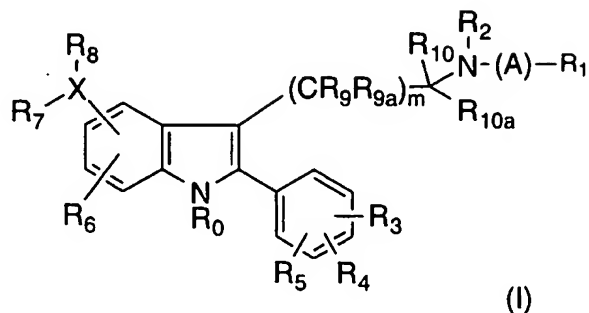


1L			
1M			
1N			
1O			
1P			
1Q			
1R			
1S			
1T			

1U			
1V			
1W			
1X			

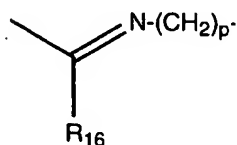
WHAT IS CLAIMED IS:

1. A compound of the formula



wherein

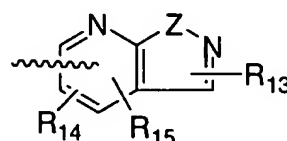
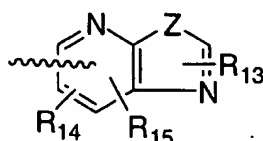
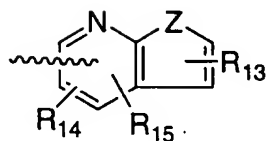
A is C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, substituted C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, substituted C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl, substituted C<sub>3</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>0</sub>-C<sub>5</sub> alkyl-S(O)<sub>n</sub>-C<sub>0</sub>-C<sub>5</sub> alkyl, C<sub>0</sub>-C<sub>5</sub> alkyl-O-C<sub>0</sub>-C<sub>5</sub> alkyl, C<sub>0</sub>-C<sub>5</sub> alkyl-NR<sub>18</sub>-C<sub>0</sub>-C<sub>5</sub> alkyl where R<sub>18</sub> and the C<sub>0</sub>-C<sub>5</sub> alkyl can be joined to form a ring,

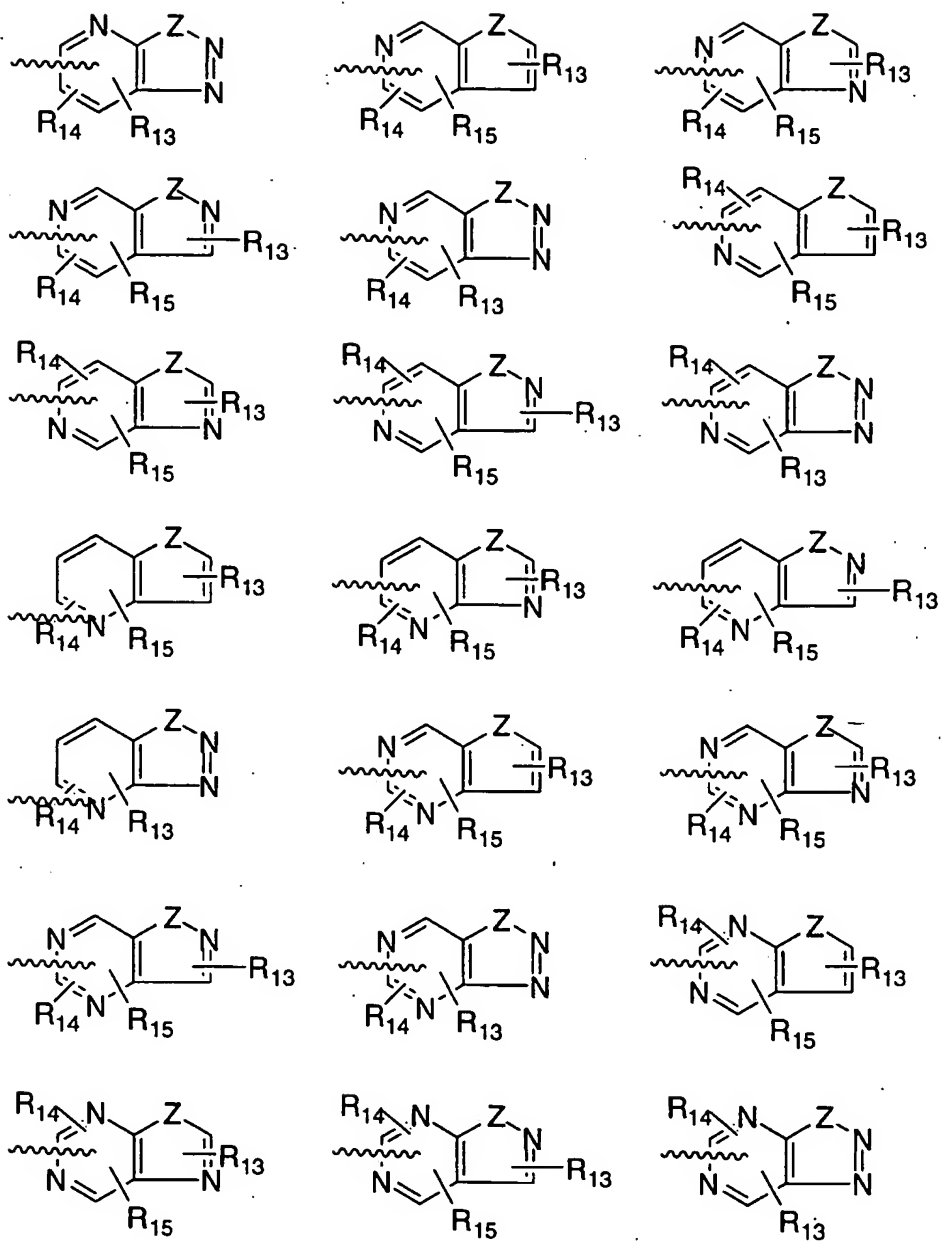


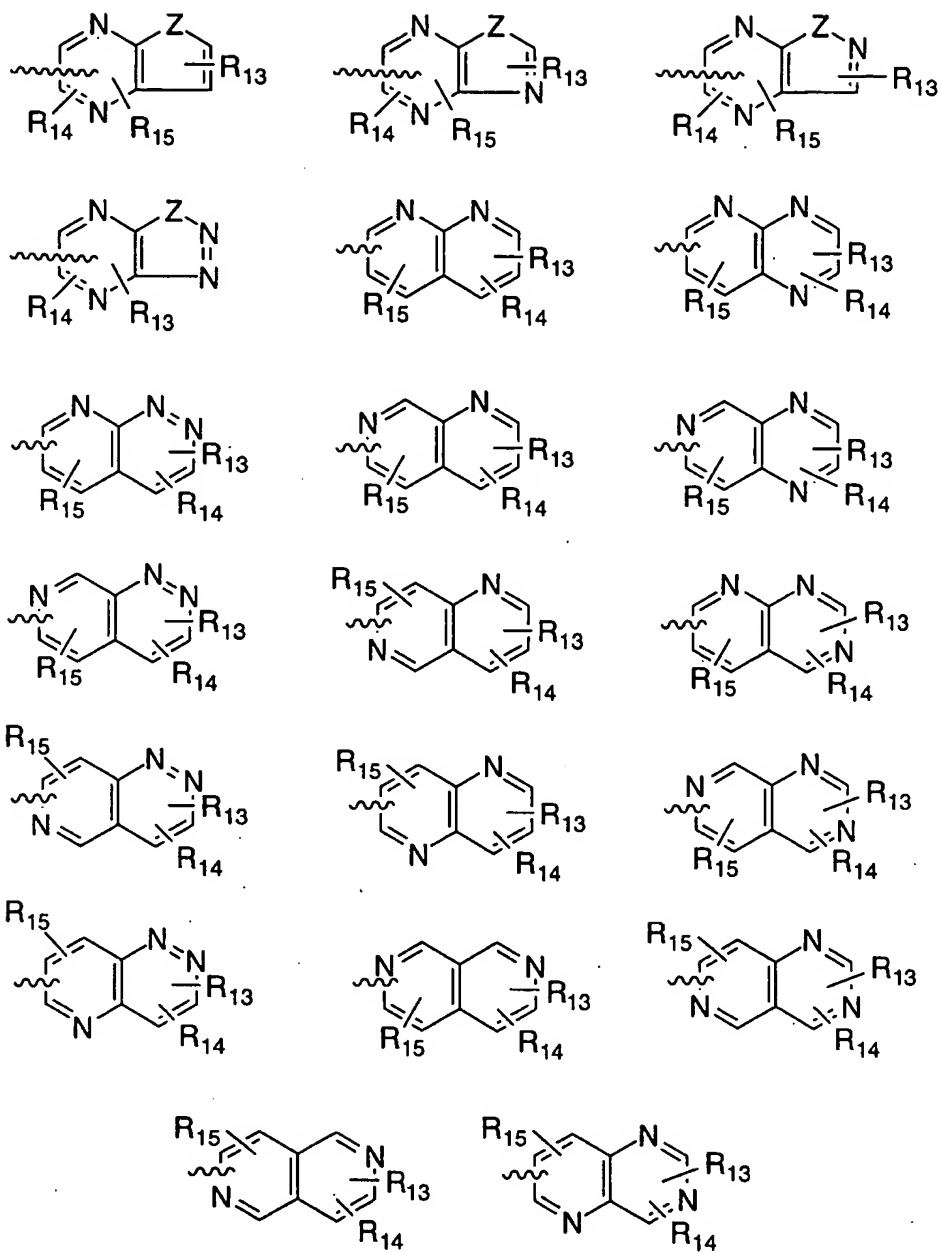
or a single bond;

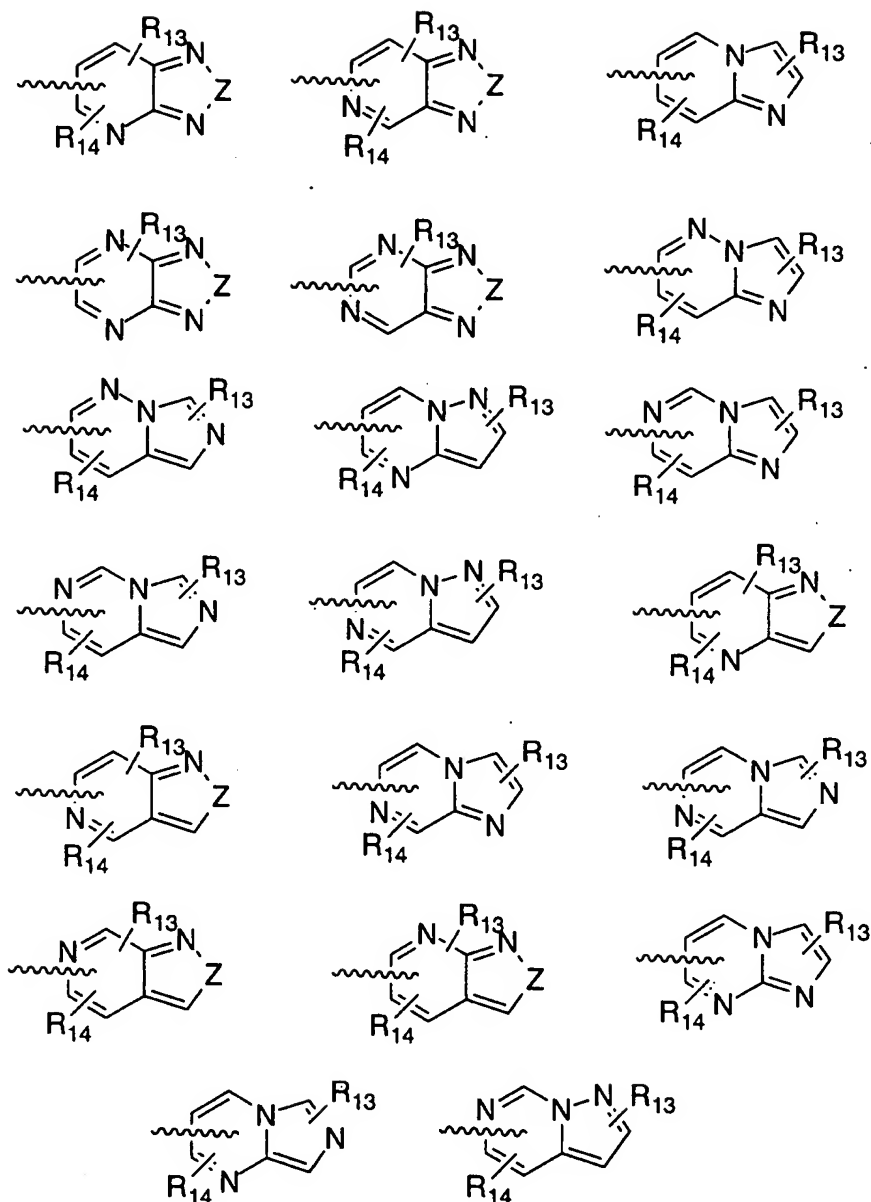
R<sub>0</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the substituents are as defined below; aryl, substituted aryl, aralkyl or substituted aralkyl, wherein the substituents are as defined for R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>;

R<sub>1</sub> is









- R<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, alkyl -OR<sub>11</sub>,  
 5 C<sub>1</sub>-C<sub>6</sub>(NR<sub>11</sub>R<sub>12</sub>), C<sub>1</sub>-C<sub>6</sub>(CONR<sub>11</sub>R<sub>12</sub>) or C(NR<sub>11</sub>R<sub>12</sub>)NH;  
 R<sub>2</sub> and A taken together form a ring of 5-7 atoms;  
 R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, CN, nitro, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkoxy, aryl,

- substituted aryl, aralkyl, substituted aralkyl,  $R_{11}O(CH_2)_p$ -,  $R_{11}C(O)O(CH_2)_p$ -,  $R_{11}OC(O)(CH_2)_p$ -,  $-(CH_2)_pS(O)_nR_{17}$ ,  $-(CH_2)_pC(O)NR_{11}R_{12}$  or halogen; wherein  $R_{17}$  is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, aryl or substituted aryl;
- 5     $R_3$  and  $R_4$  taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing 1-3 heteroatoms selected from N, O and S;
- $R_6$  is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, CN, NO<sub>2</sub>, halogen,  $R_{11}O(CH_2)_p$ -,  $NR_{21}C(O)R_{20}$ ,  $NR_{21}C(O)NR_{20}R_{21}$  or  $SO_nR_{20}$ ;
- 10     $R_7$  is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, unless X is hydrogen or halogen, then  $R_7$  is absent;
- $R_8$  is  $C(O)OR_{20}$ ,  $C(O)NR_{20}R_{21}$ ,  $NR_{20}R_{21}$ ,  $C(O)R_{20}$ ,  $NR_{21}C(O)R_{20}$ ,  $NR_{21}C(O)NR_{20}R_{21}$ ,  $NR_{20}S(O)_2R_{21}$ ,  $NR_{21}S(O)_2NR_{20}R_{21}$ ,  $OC(O)R_{20}$ ,  $OC(O)NR_{20}R_{21}$ ,  $OR_{20}$ ,  $SO_nR_{20}$ ,  $S(O)_nNR_{20}R_{21}$ , a
- 15    heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by  $R_3$ ,  $R_4$  and  $R_5$ , C<sub>1</sub>-C<sub>6</sub> alkyl or substituted C<sub>1</sub>-C<sub>6</sub> alkyl; or
- 20     $R_7$  and  $R_8$  taken together form a heterocyclic ring containing one or more heteroatoms selected from N, O or S which can be optionally substituted by  $R_3$ ,  $R_4$  and  $R_5$ ;
- $R_9$  and  $R_{9a}$  are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl; aryl or substituted aryl, aralkyl or substituted aralkyl
- 25    when m is not equal to 0; or
- $R_9$  and  $R_{9a}$  taken together form a carbocyclic ring of 3-7 atoms or  $\overset{O}{\parallel}$  when m is not equal to 0;
- $R_9$  and A taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms when m is not equal to
- 30    0; or
- $R_{10}$  and  $R_{10a}$  are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl; or

- R<sub>10</sub> and R<sub>10a</sub> taken together form a carbocyclic ring of 3-7 atoms or  $\text{O}=\text{C}$  ;  
 R<sub>9</sub> and R<sub>10</sub> taken together form a carbocyclic ring of 3-7 carbon atoms or  
 a heterocyclic ring containing one or more heteroatoms  
 when m is not equal to 0; or
- 5 R<sub>9</sub> and R<sub>2</sub> taken together form a heterocyclic ring containing 3-7 carbon  
 atoms and one or more heteroatoms when m is not equal to  
 0; or
- R<sub>10</sub> and R<sub>2</sub> taken together form a heterocyclic ring containing 3-7 carbon  
 atoms and one or more heteroatoms;
- 10 R<sub>10</sub> and A taken together form a heterocyclic ring containing 3-7 carbon  
 atoms and one or more heteroatoms; or
- R<sub>11</sub> and R<sub>12</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted  
 C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, substituted aryl, aralkyl, substituted  
 aralkyl, a carbocyclic ring of 3-7 atoms or a substituted  
 15 carbocyclic ring containing 3-7 atoms;
- R<sub>11</sub> and R<sub>12</sub> taken together can form an optionally substituted ring of  
 3-7 atoms;
- R<sub>13</sub> is hydrogen, OH, NR<sub>7</sub>R<sub>8</sub>, NR<sub>11</sub>SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl),  
 NR<sub>11</sub>SO<sub>2</sub>(substituted C<sub>1</sub>-C<sub>6</sub> alkyl), NR<sub>11</sub>SO<sub>2</sub>(aryl),  
 20 NR<sub>11</sub>SO<sub>2</sub>(substituted aryl), NR<sub>11</sub>SO<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl);  
 SO<sub>2</sub>NR<sub>11</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), SO<sub>2</sub>NR<sub>11</sub>(substituted C<sub>1</sub>-C<sub>6</sub> alkyl),  
 SO<sub>2</sub>NR<sub>11</sub>(aryl), SO<sub>2</sub>NR<sub>11</sub>(substituted aryl), SO<sub>2</sub>NR<sub>11</sub>(C<sub>1</sub>-C<sub>3</sub>  
 perfluoroalkyl); SO<sub>2</sub>NR<sub>11</sub>(C(O)C<sub>1</sub>-C<sub>6</sub> alkyl); SO<sub>2</sub>NR<sub>11</sub>(C(O)-  
 substituted C<sub>1</sub>-C<sub>6</sub> alkyl); SO<sub>2</sub>NR<sub>11</sub>(C(O)-aryl);  
 25 SO<sub>2</sub>NR<sub>11</sub>(C(O)-substituted aryl); S(O)<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl);  
 S(O)<sub>n</sub>(substituted C<sub>1</sub>-C<sub>6</sub> alkyl), S(O)<sub>n</sub>(aryl), S(O)<sub>n</sub>(substituted  
 aryl), C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkoxy, C<sub>1</sub>-C<sub>6</sub>  
 alkoxy, substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, COOH, halogen, NO<sub>2</sub> or  
 CN;
- 30 R<sub>14</sub> and R<sub>15</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub>  
 alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, CN, nitro,  
 C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl, C<sub>1</sub>-C<sub>3</sub> perfluoroalkoxy, aryl,

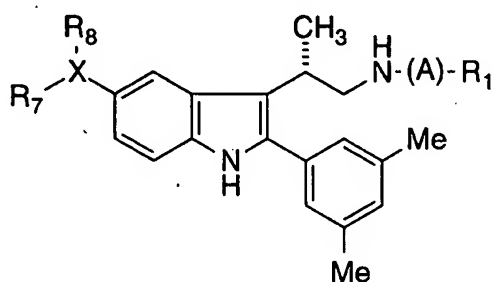


- substituted aryl, aralkyl, substituted aralkyl,  $R_{11}O(CH_2)_p-$ ,  $R_{11}C(O)O(CH_2)_p-$ ,  $R_{11}OC(O)(CH_2)_p-$ ,  $-(CH_2)_pS(O)_nR_{17}$ ,  $-(CH_2)_pC(O)NR_{11}R_{12}$  or halogen; wherein  $R_{17}$  is hydrogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_3$  perfluoroalkyl, aryl or substituted aryl;
- 5  $R_{16}$  is hydrogen,  $C_1$ - $C_6$  alkyl, substituted  $C_1$ - $C_6$  alkyl, or  $N(R_{11}R_{12})$ ;
- $R_{18}$  is hydrogen,  $C_1$ - $C_6$  alkyl, substituted  $C_1$ - $C_6$  alkyl,  $C(O)OR_{11}$ ,  $C(O)NR_{11}R_{12}$ ,  $C(O)R_{11}$ ,  $S(O)_nR_{11}$ ;
- $R_{19}$  is either the definition of  $R_{13}$  or  $R_{14}$ ;
- 10  $R_{20}$  and  $R_{21}$  are independently hydrogen,  $C_1$ - $C_6$  alkyl, substituted  $C_1$ - $C_6$  alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic ring of 3-7 atoms, a substituted carbocyclic ring containing 3-7 atoms, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms
- 15 selected from N, O or S which can be optionally substituted by  $R_3$ ,  $R_4$  and  $R_5$ ,  $C_1$ - $C_6$ -alkyl substituted by a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by  $R_3$ ,  $R_4$  and  $R_5$ ;
- 20  $R_{20}$  and  $R_{21}$  taken together can form an optionally substituted ring of 3-7 atoms;
- $X$  is N, O,  $S(O)_n$ ,  $C(O)$ ,  $(CR_{11}R_{12})_p$ , a single bond to  $R_8$ ,  $C_2$ - $C_6$  alkenyl, substituted  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, or substituted  $C_2$ - $C_6$  alkynyl; when  $X$  is O,  $S(O)_n$ ,  $C(O)$ , or
- 25  $CR_{11}R_{12}$  only  $R_8$  is possible;
- $Z$  is O, S or  $NR_{11}$ ;
- $m$  is 0-3;
- $n$  is 0-2;
- $p$  is 0-4; and
- 30 the alkyl, cycloalkyl, alkenyl and alkynyl substituents are selected from  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_7$  cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, hydroxy, oxo, cyano,  $C_1$ - $C_6$  alkoxy, fluoro,  $C(O)OR_{11}$ , aryl  $C_1$ - $C_3$  alkoxy, substituted aryl

C<sub>1</sub>-C<sub>3</sub> alkoxy, and the aryl substituents are as defined for R<sub>3</sub>,  
R<sub>4</sub> and R<sub>5</sub>;

or a pharmaceutically acceptable addition salt and/or hydrate thereof, or  
where applicable, a geometric or optical isomer or racemic mixture  
thereof.

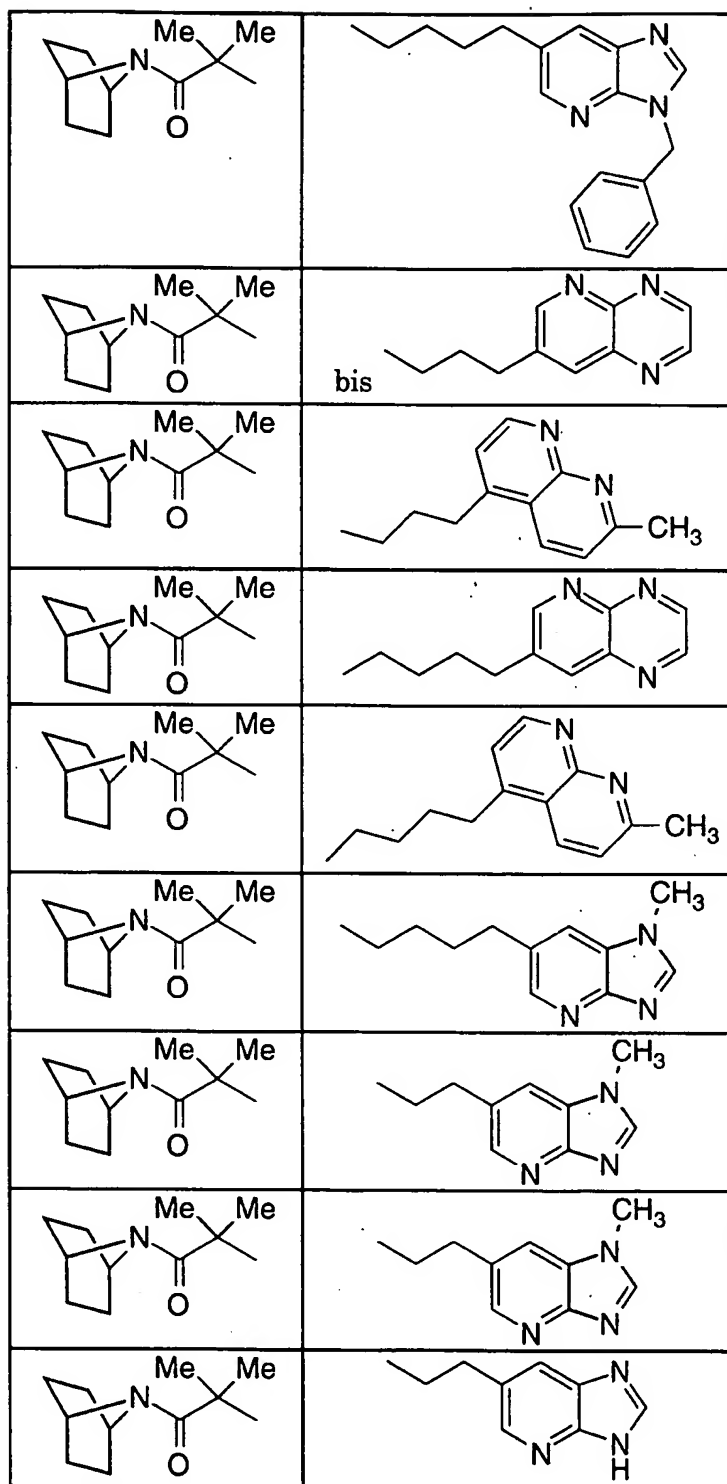
2. The compound according to Claim 1 of the formula

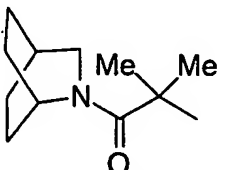
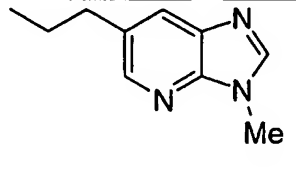
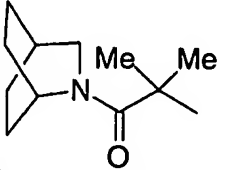
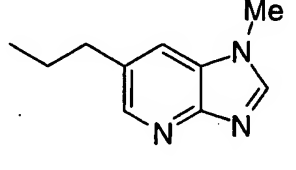
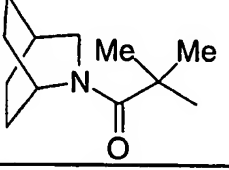
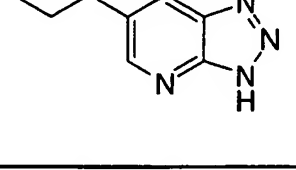
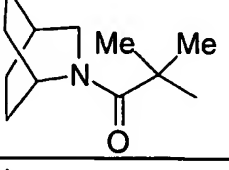
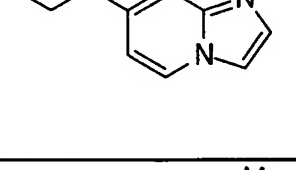
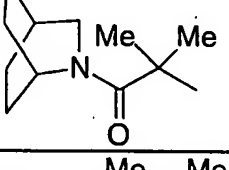
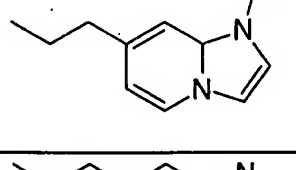
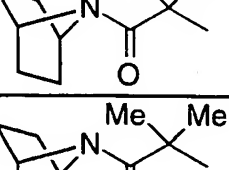
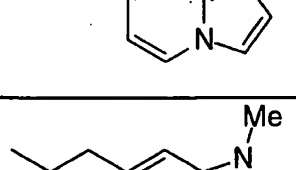
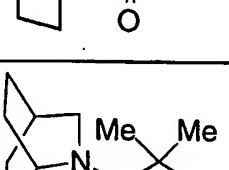
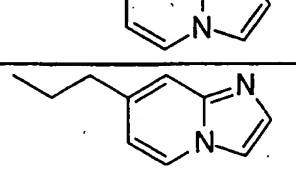
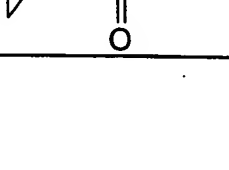
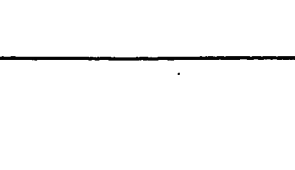


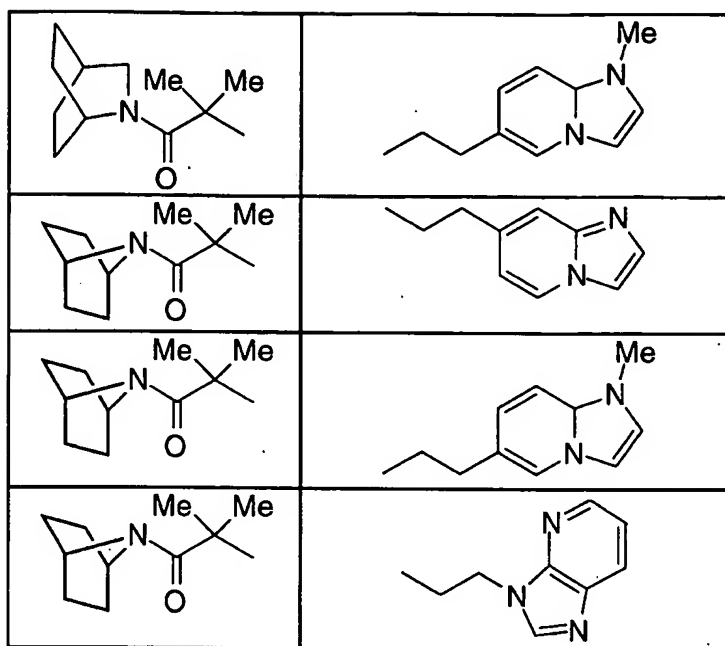
wherein A, R<sub>1</sub> and X-R<sub>7</sub>,R<sub>8</sub> are as indicated in the table below:

10

X-R <sub>7</sub> ,R <sub>8</sub>	-(A)-R <sub>1</sub>





3. A pharmaceutical composition which comprises an effective amount of a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

5

4. A method for antagonizing gonadotropin-releasing hormone in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1 to a subject suffering from a gonadotropin-releasing hormone derived disorder.

10

5. A method according to Claim 4 wherein the gonadotropin-releasing hormone derived disorder is a sex-hormone related condition.

15

6. A method according to Claim 4 wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus.

7. A method according to Claim 6 wherein the sex hormone dependent cancer is selected from the group consisting of prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenomas.

5

8. A method according to Claim 5 wherein the sex hormone related condition is selected from the group consisting of endometriosis, polycystic ovarian disease, uterine fibroids and precocious puberty.

10

9. A method for preventing pregnancy in a subject in need thereof which comprises administering an effective amount of a compound as defined in Claim 1.

15

10. A method for treating lupus erythematosus in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

20

11. A method for treating irritable bowel syndrome in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

25

12. A method for treating premenstrual syndrome in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

30

13. A method for treating hirsutism in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

35

14. A method for treating short stature or a growth hormone deficiency in a subject in need thereof which comprises administering to said subject an effective amount of a compound which stimulates the endogenous production or release of growth hormone and an effective amount of a compound as defined in Claim 1.

15. A method for treating sleep disorders in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

5

16. The method of Claim 15 wherein the sleep disorder is sleep apnea.

17. A mammographic method in which the image on the  
10 mammographic film has enhanced readability relative to a mammogram effected in the absence of the method, which comprises administering to a premenopausal woman an effective amount of a compound as defined in Claim 1.

18. A pharmaceutical composition which comprises an inert carrier and an effective amount of a compound which stimulates the endogenous production or release of growth hormone in combination with a compound as defined in Claim 1.

19. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier therefor.

20. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

21. Pharmaceutical therapy comprising co-administration of a compound having luteinizing hormone releasing  
30 hormone activity with a compound of Claim 1.

22. The therapy of Claim 21 wherein the compound having luteinizing hormone releasing hormone activity is a peptide compound.

35

23. The therapy of Claim 22 wherein the peptide compound is a natural hormone or an analog thereof.

5 24. The therapy of Claim 22 wherein the peptide compound is a compound selected from the group consisting of leuprorelin, gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterelin and recirelin.

10 25. Pharmaceutical combination therapy comprising a compound having luteinizing hormone releasing hormone activity in combination with a compound of Claim 1.

15 26. The therapy of Claim 25 wherein the compound having luteinizing hormone releasing hormone activity is a peptide compound.

27. The therapy of Claim 26 wherein the peptide compound is a natural hormone or an analog thereof.

20 28. The therapy of Claim 26 wherein the peptide compound is a compound selected from the group consisting of leuprorelin, gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterelin and recirelin.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/02906

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : C07D 401/12, 215/06, 471/04, 487/06

US CL : 546/17, 18, 121, 122, 176; 544/236

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/17, 18, 121, 122, 176; 544/236

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,849,764 A (GOULET et al.) 15 December 1998, col. 3, lines 20-35.	1-28
X, P	US 5,756,507 A (GOULET et al.) 26 May 1998, col. 3, lines 15-30.	1-28

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 JUNE 1999

Date of mailing of the international search report

21 JUL 1999

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

DOMINIC KEATING

Telephone No. (703) 308-1234

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/02906

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/02906

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, the invention according to claim 1, formula I, wherein R1 is pyridotriazine or pyridopyrazole.

Group II, the invention according to claim 1, formula I, wherein R1 is pyridopyrazine.

Group III, the invention according to claim 1, formula I, wherein R1 is imidazopyridine.

Group IV, the invention according to claim 1, formula I, wherein R1 is naphthyridine.

Group V, the invention according to claim 1, formula I, wherein R1 is isoquinoline or quinoline.

Claims 1-28 will be examined, commensurate in scope with the elected invention.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The common core is a phenyl substituted indole. This core is known in the art and therefore cannot be the special technical feature. The substituents in the R1 position, such as the pyridotriazine and the naphthyridine, do not related to a single inventive concept.